

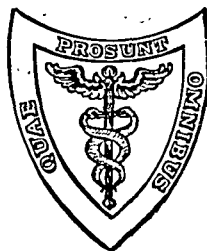
THE
AMERICAN JOURNAL
OF THE
MEDICAL SCIENCES

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NEW SERIES

VOL. 211



LEA & FEBIGER
PHILADELPHIA

1946

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PRINTED IN U. S. A.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JANUARY, 1946

ORIGINAL ARTICLES

PREFRONTAL LOBOTOMY

SURVEY OF 331 CASES

BY WALTER FREEMAN, M.D., PH.D., F.A.C.P.

AND

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PREFRONTAL lobotomy represents in some respects the most drastic treatment yet devised for the handling of intractable psychoses and neuroses. Whereas shock methods with insulin, metrazol and electroshock have been shown to produce certain damaging effects upon the brain, they can scarcely be compared, pathologically, with the lesions produced by severing the connections between the thalamus and the frontal lobes of the brain. By the same token, however, prefrontal lobotomy produces therapeutic results in cases that have been unsuccessfully treated by long series of shocks. We believe that there is something specific in the attack upon this region of the brain, something that is not achieved by the general disruption of cortical processes that is accomplished by shock therapies. The comparison has been suggested of the rifle bullet as compared with the shotgun charge.

The surgical treatment of mental disorders was initiated a decade ago by Egas Moniz,³ following the demonstration in man and in animals that a considerable portion of the frontal lobes could be removed without danger to life, and with preservation of most of the intellectual functions.^{2,12}

Egas Moniz reasoned that the stereotyped behavior patterns observed in the course of certain "functional" mental disorders could be occasioned by pathologic stabilization of synaptic connections of cortical cell groups. "In accordance with the theory which we have just developed," he writes, "one conclusion is derived; to cure these patients we must destroy the more or less fixed arrangements of cellular connections that exist in the brain, and particularly those which are related to the frontal lobes." Egas Moniz reported 7 recovered and 7 improved among his first 20 patients.

Early in our work we were impressed with the subtle change that took place in patients thus operated upon. Disproving Egas Moniz' ideas, at least in part, these patients continued to manifest their same hallucinations and delusions, but were no longer bothered by them. It was the emotional reaction to the ideas that had been suppressed. When this fact was more fully investigated it was realized that the incisions in the frontal lobes interrupted the anterior thalamic radiation as described by Herrick,¹¹ and actually produced degeneration in the nucleus medialis dorsalis of the thalamus as found by

Walker¹⁸ in lobectomized monkeys. This radiation is clearly seen in some of Flechsig's⁵ charts, having become myelinated long before the association pathways in the same area.

Clinical studies on patients with lesions of the frontal lobes, and investigations upon animals whose frontal lobes had been removed^{2,4,10,12,13,14} dealt largely with intellectual functions. The results were far from uniform, but the "best" cases showed so little impairment of intelligence as measured by the tests employed that further inquiry into the functions of the frontal lobes was stimulated. Such investigations could be carried out substantially only in man because of the necessity for securing the maximum interplay of ideas between investigator and subject. Fortunately a sufficient number of patients have been studied now, before and after prefrontal lobotomy, to lend some weight to the hypothesis that was elaborated in the early stages of our⁷ studies. Fundamentally, we believe that the frontal lobes subserve the functions of foresight and insight, particularly as related to the self. It is in relation to these ego functions that the affective coloring supplied by the thalamus is of overwhelming importance for the adjustment of the individual in his social milieu.

This report deals with some 300 patients who have been observed over a period of from 6 months to 9 years following prefrontal lobotomy. Emphasis is placed upon the social adjustment, in terms of working capacity and ability to live outside an institution. It also takes up the question of how much frontal lobe tissue must be sacrificed in order to eliminate the affective component that keeps the psychosis alive, and how much must be retained in order to preserve the ability of the individual to function adequately in the world of his fellows. Multiple operations have enabled us to form some opinions in regard to this all-important question, and the search for the "ideal" plane of section still goes forward. There is some hope that future investigations

may make it possible to attack certain restricted areas of the brain for the relief of circumscribed ideational and behavioral abnormalities, such as hypochondriasis or obsessive-compulsive reactions. At the present time, however, we are inclined to operate on the working hypothesis that the results of operation depend upon the number of fibers severed in the anterior thalamic peduncle, and we endeavor to place the incisions so as to strike the proper balance between the abolition of the disabling psychosis and the preservation of capacity for productive work.

Operative Procedure. The surgical aspects of prefrontal lobotomy have been described.⁹

Burr holes are made through the coronal suture on each side about 6 cm. above the zygoma and are enlarged along the suture by means of a rongeur. The dura is then opened, hemostasis secured and the cortex punctured in an avascular area. The surgeon measures the diameter of the frontal lobes by passing a long cannula from one opening in the skull through the brain and out the other opening. At this location the frontal lobe varies between 4.5 and 5.5 cm. in diameter. The surgeon withdraws the cannula and angulates it downward delicately probing until he can positively identify the sphenoidal ridge. This gives an important landmark for precise surgery.

The surgeon removes the cannula and replaces it with a blunt knife inserting it to a depth 1 cm. short of the midline and then swinging it through an arc, first downward, then upward, through the frontal lobe. Here the surgeon relies constantly for orientation upon marks upon the scalp and upon guidance by the neurologist in order to remain accurately in the plane of the coronal suture. The ventricles can be entered without any harm. After irrigation of the incisions to control what little bleeding there may be, the surgeon returns the knife to the incisions, and by making radial thrusts or stabs, still under control by the neurologist, deepens the incisions to the base of

the frontal lobe, and as far as the midline. These stab incisions sever the white matter but displace the arteries on the mesial surface rather than lacerate them. Before closing the dura and scalp the surgeon finally injects a small quantity of iodized oil into the depths of the incisions, and after applying the dressing, marks on the bandage the location of the operative incisions underneath so that the technician may be able to take the roentgenograms as nearly as possible superimposing the burr holes in one of the stereoscopic lateral views. (Fig. 1.) An occipitofrontal view is also of value in order to indicate the depth of the incisions.

the sphenoidal ridge at the lower end, but it can be done, and its importance is stressed by the fact that deviations of 5 mm. one way or the other from the selected plane may make the difference between success and failure of the operation, or even death.

There are several factors that enter into the decision as to where to make the incisions in relation to the coronal suture. The most important of these is the duration of the psychosis. We conceive the psychosis in terms suggested by Egas Moniz, namely, the pathologic stabilization of synaptic patterns among various cell groups, particularly in the frontal

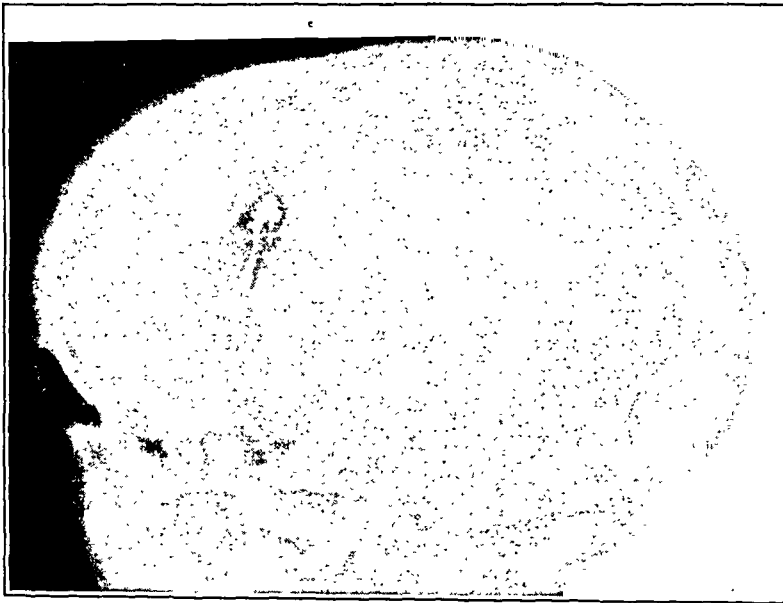


FIG. 1.—Roentgenogram after prefrontal lobotomy in plane of coronal suture outlined by iodized oil. Recovery from agitated depression after electroshock failed.

While incisions in the plane of the coronal suture yield good results in most cases of involutional depression or psychoneurosis, they are apt to be followed by only temporary improvement in schizophrenics. Relapses were so frequent, indeed, among our early cases that after many cases coming to secondary operation we arrived at a plan of fitting the incisions to the individual case. It requires precise surgery to cut the subcortical white matter in a plane, say, 8 mm. behind the coronal suture at the upper end and 5 mm. behind

lobes. With the development and fixation of the psychosis, we suggest that there occurs through the process of facilitation the inclusion of a progressively larger number of cortical cell population into the pattern of behavior. If this hypothesis is correct, it is likely that the spread of the abnormal stabilization is in a posterior direction, and that it comes to include mechanisms that are concerned in the ordinary everyday adaptations to social existence. Consequently, if the psychosis is of long duration and associated with

severe deviations from acceptable social behavior, the incisions must be placed so that the cell complexes underlying the dominant form of behavior can be cut off from their thalamic component. In other words the energizing emotional force in the psychosis must be cut down sufficiently to allow the other aspects of the personality to escape from dominance by the psychotic process. Prefrontal lobotomy fails in deteriorated cases largely because the operation cannot be carried out sufficiently far posteriorly to interrupt the psychosis without at the same time extinguishing those emotional factors that make for satisfactory adaptation in a normal social environment. A deteriorated schizophrenic looks and acts about the same with or without his frontal lobes.

Another factor in determining the location of the plane of the incisions is the age of the patient. In general older patients react more favorably to incisions placed anteriorly. In these cases, presumably, the behavior patterns of social existence have been stabilized for decades, and the psychosis is a development of the later period, so that a conservative operation produces sufficient reduction in the emotional toning of the psychotic process and still leaves the individual enough of the anatomic connections so that a good adaptation is possible. We have also been impressed with the large amount of frontal lobe that can be sacrificed in youthful individuals with eventual return to a satisfactory social adaptation. After severing the direct thalamic connections to a fairly large proportion of the frontal regions, there are still indirect connections that make for more adequate behavior after abolition of pathologic mechanisms persisting from the psychosis. Particularly interesting is the long continued process of adaptation in youthful individuals once the emotional nucleus of the psychosis has been eliminated. Improvement may be expected for at least 3 years and often more.

Contrary to our earlier conclusions, hypochondriasis and fixation of visceral

complaints in involutional depressions have been satisfactorily overcome by a standard operative procedure, but a severe obsessive compulsive neurosis of long duration may require incisions from 5 to 7 mm. posterior to the plane of the coronal suture. Long-standing schizophrenia requires the maximum operation. In such cases we usually operate from above, through burr holes 10 to 15 mm. behind the coronal suture and 4 cm. from the midline, carrying the incisions down to the sphenoidal ridge or even angulating backward a little so as to reach the base of the frontal lobe 7 to 10 mm. behind the sphenoidal ridge. (Fig. 2.)

Emphasis is placed upon the variations in the procedure of prefrontal lobotomy because the success or failure of operation may depend upon a very few millimeters of tissue in the frontal lobe. We have re-operated upon some patients as long as 5 years after the primary intervention because of relapse into psychotic behavior. On the other hand, some patients have given every evidence of complete and permanent disability up to the present time several years after placement of incisions too far posteriorly. As stated previously, in order to obtain satisfactory results sufficient fibers must be severed in order to reduce the emotional component of the psychosis to the point where the ideas no longer dominate the behavior of the patient, yet the incisions must leave sufficient quantities of the frontal lobes in order to permit the patient to make a satisfactory adaptation in a social environment. Every millimeter that the incisions trespass upon the area posterior to the plane of the coronal suture renders this adaptation less complete and more difficult.

Certain aids in convalescence and rehabilitation have been described by us.⁸ There are means of combating certain symptoms that have not been stressed previously. Convulsive seizures respond fairly well to a combination of phenytoin and phenobarbital in a dosage determined by the individual case. The medication should be continued until 2 years have

elapsed from the latest attack. Sometimes, however, 3 years may intervene between attacks. Urinary frequency and urgency with occasional incontinence have sometimes yielded to atropine and ephedrine in appropriate dosage. Inertia finds a suitable remedy in amphetamine sulphate in doses as high as 30 mg. daily. Electroshock therapy has been useful in mild relapses especially in the involutional depressions. Usually two or three shocks are sufficient to relieve the obsessive preoccupation in a way that was impossible previous to lobotomy. If the relapse is

they have been too preoccupied with themselves, following operation they are at the mercy of every passing external stimulus. The emotional intensity characteristic of the psychosis gives way to the emotional shallowness of the postoperative state, and the imaginative activity which was at its height during the psychosis undergoes more or less permanent reduction. Patients who have made a satisfactory recovery, however, and this includes the majority of those operated on, are far from inanimate clods. They are cheerful, friendly, uncomplaining, outspoken, buoy-



FIG. 2.—Roentgenogram after 2 prefrontal lobotomies, first in the plane of the coronal suture, second (4 mos. later) 1 cm. behind it. Patient was a violent tuberculous schizophrenic hospitalized for 5 years who subsequently gained 25 kg., healed in his tuberculosis and soon will be paroled to his family.

stubborn, however, reoperation is undertaken without delay. Weight control is a matter of calories and may require padlocks on the refrigerator. Amphetamine, however, not infrequently brings the appetite within bounds. This drug is also more useful than phenobarbital in the control of restlessness and irritability.

It goes without saying that patients who have been operated on are far from healthy, particularly at first. In undergoing prefrontal lobotomy they have exchanged one form of abnormal behavior for another. Whereas during the psychosis

ant, for the most part. They fall in with the mood of their companions, are quick to follow suggestions and are not embarrassed, glum or self-conscious. They take an active interest in everything that goes on about them, read the papers, attend movies, work regularly and play games with intelligence and foresight. With them the emotional component of foresight and insight is sufficient for meeting external situations of moderate complexity. It seems, however, that introversional preoccupation is no longer possible. If asked about themselves and their previous

troubles they may recall various ideas or particular episodes, but without concern, and many patients have a more or less complete amnesia for the whole psychotic period that may be of many years' duration. This last fact was stressed particularly by Strecker, Palmer and Grant.¹⁶

Results. In Table 1 is given the present status of 260 patients who have been followed from 6 months to 9 years following prefrontal lobotomy, divided according to the main diagnostic groups. All of the patients have been seen or reported on during 1945. It will be seen that patients with psychoneuroses offer the best outlook as far as employment is concerned. These individuals are intelligent and possessed of a satisfactory energy component. Their difficulties in postoperative adaptation come from too great a tendency to aggres-

markable therapeutic procedure for the relief of mental pain.

Schizophrenia presents numerous problems that are far from solution. However, with every review of the schizophrenic patients undergoing prefrontal lobotomy we are more encouraged. It stands to reason that the results in terms of employability are inferior to those in the neurotic category, but the number of patients that are now at home after prolonged residence in mental hospitals is encouraging. Moreover a considerable number of patients are self-sustaining and with the lapse of time are improving rather than retrogressing. Prefrontal lobotomy is of particular value in the chronically disturbed and overactive schizophrenic as reported by several observers.¹ We now have several patients under observation at St.

TABLE 1.—STATUS OF LIVING PATIENTS, JUNE 1945, 6 MONTHS TO 9 YEARS FOLLOWING PREFRONTAL LOBOTOMY

Disease	No.	Regularly employed, %	Partly employed, %	Keeping house, %	At home, %	In hospital, %
Involuntional psychoses	83	10	6	43	25	16
Schizophrenias	96	29	9	8	28	26
Obsessive states	43	51	11	14	12	12
Psychoneuroses	35	46	3	26	20	5
Unclassified	3	67	33
Totals	260	30	8	22	23	17

sive behavior, which is gradually toned down in the years following operation. Patients with involuntional depressions and psychoses achieve a satisfactory degree of relief from their painful ideas, but in many instances they have reached the age of retirement from business, or are no longer active in the management of the household. One patient, however, worked as a bookkeeper for 8 years following prefrontal lobotomy, and then, becoming bored with retirement after a few months, went back to work at her same job. Patients with involuntional depression are very deserving of help by psychosurgery if other methods fail. Most of our cases in this category have either had previous shock therapy without relief, or because of physical complications have been considered unsuitable candidates. Prefrontal lobotomy is a re-

Elizabeths Hospital who were operated upon during the past 2 years. They were of the type that requires constant seclusion because of shouting, spitting, smearing and assaultive behavior. From 3 to 5 attendants were sometimes required to administer medicines and even food. Without good care these patients would have killed themselves through frenzy and exhaustion. These patients are now still in the hospital for the most part, but are clothed decently, eating with other patients, tractable and no longer troublesome or dangerous to the ward personnel. The saving to the hospital in wear and tear is considerable. One of the medical officers (W. W. Eldridge) is particularly gratified at the results in the disturbed tuberculous schizophrenics who represent an additional menace to their comrades and attendants

by spitting freely. Studies have shown that in these patients the postoperative period is characterized by a gain in weight up to 20 kg. and by progressive healing of the tuberculous process in the lungs.

Prefrontal lobotomy for the relief of pain is a subject that is under investigation. Patients have been operated upon successfully for the relief of tabetic pains, inoperable carcinoma, trauma to the cauda equina and thalamic syndrome. Relief of pain in phantom limb has been reported.¹⁷ In these cases it would seem that the emotional component, the fear of pain, is vanquished, and that peace of mind is a big factor in the greater comfort secured by the patients.

Chronic alcoholism is not relieved by prefrontal lobotomy. Neither is epilepsy,

employed, and may be freed from his mental disturbance, but still be considered a poor result because of his inability to get along harmoniously with his relatives because of unleashed aggressiveness that makes life miserable for them. On the other hand, a patient may still require hospital treatment but be considered a good result because of the cessation of disturbed behavior as described above. Some of the poor results stem from too limited an operation, with persistence of symptoms and no opportunity for further operation; some from operating upon patients whose deterioration had progressed too far to allow of a comeback under any known circumstances; and some from too extensive an operation, reducing the individual to permanent childish dependency,

TABLE 2.—RESULTS OF PREFRONTAL LOBOTOMY (SEPTEMBER 1936 TO JUNE 1945)

Disease	No.	Results				Recent cases†
		Good, %	Fair, %	Poor, %	Deaths,* %	
Involuntional psychoses	108	50	31	16	3	10
Schizophrenias	126	46	36	16	2	25
Obsessive states	51	61	35	..	4	5
Psychoneuroses	38	63	29	8	..	3
Unclassified	8	25	12	25	38	—
Totals	331	52	32	13	3	43

* Operative deaths only. Individuals dying subsequent to operation (18) have been listed according to results, good, fair or poor, during their postoperative term of life.

† Recent cases (shown by number) have not been included in the percentage tabulation.

although there are some reports of success in cases of dangerous epileptic furors and other complications of epilepsy.¹⁶ Parkinsonism remains unchanged; in fact a patient has recently developed this disease 6 years after prefrontal lobotomy for an involuntional depression at which time there was no hint of the disease. One patient with probable multiple sclerosis and severe emotional disturbances requiring hospitalization has been employed for a year and has shown improvement rather than advance of the disease.

Table 2 gives an estimate of the results of prefrontal lobotomy on the basis of 331 cases operated upon up to the present time. In estimating the results, the former condition of the patient has been kept in mind. For instance, a patient may be

On the whole, however, the good results outweigh the bad. Prefrontal lobotomy is a relatively safe operation, the operative mortality being under 3%, and it can be carried out in patients whose physical condition precludes other drastic forms of treatment.

Conclusions. Prefrontal lobotomy has been performed by us in 331 cases during the past 9 years. Refinements of the operative procedure have given us a controllable and accurate means of severing the thalamofrontal radiation in such a manner that in a high percentage of the cases the emotional component of the neurosis or psychosis can be reduced to the point of tolerability without sacrificing too much of the individual's ability to adapt himself to life outside an institution.

This surgical procedure is to be employed only in cases in which a favorable outcome is not to be anticipated under more conservative measures. It should not be postponed too long, however, since deterioration may progress to the point where operation will no longer be serviceable.

The most favorable results are obtained in obsessive tension states, with or without compulsions, in hypochondriasis and intractable psychosomatic conditions, and in agitated depressions. Less satisfactory results are obtained in schizophrenias, although as long as the patient is fighting

his disease there still remains the possibility of satisfactory modification of his disturbed behavior. Alcoholism, paranoid states and psychoses with organic brain diseases yield rather poor results. The treatment of structurally conditioned painful disorders is giving favorable results.

The most important sequels are inertia, aggressiveness, and epileptic seizures, but these are disabling in only a minor percentage of cases.

About half the patients are usefully occupied, one-quarter remain at home and one-quarter are dead or institutionalized.

REFERENCES

1. BENNETT, A. E., KEEGAN, J. J., and WILBUR, C. B.: J. Am. Med. Assn., **123**, 809, 1943.
2. BRICKNER, R. M.: Intellectual Functions of the Frontal Lobes, New York, Macmillan, 1936.
3. EGAS MONIZ: Tentatives opératoires dans le traitement de certaines psychoses, Paris, Masson, 1936.
4. FEUCHTWANGER, E.: Die Funktionen des Stirnhirns, Monogr. a. d. Grenzgeb. d. Neurol. u. Psychiat., Berlin, Springer, 1923.
5. FLECHSIG: Anatomie des menschlichen Gehirns und Rückenmarks auf myelogenetischer Grundlage, Leipzig, Thieme, 1920.
6. FREEMAN, W., and WATTS, J. W.: Psychosurgery, Springfield, Thomas, 1942.
7. FREEMAN, W., and WATTS, J. W.: Yale J. Biol. and Med., **11**, 527, 1939.
8. FREEMAN, W., and WATTS, J. W.: Am. J. Psychiat., **99**, 798, 1943.
9. WATTS, J. W., and FREEMAN, W.: J. Internat. Coll. Surg., **5**, 233, 1942.
10. GOLDSTEIN, K.: J. Neurol. and Psychopathol., **17**, 27, 1936.
11. HERRICK, C. J.: Brains of Rats and Men, Chicago, Univ. of Chicago Press, 1926.
12. JACOBSEN, C. F.: Studies on Cerebral Function in Primates, Comp. Psychol. Monogr., vol. **13**, No. 3, 1936.
13. KLEIST, K.: Kriegsverletzungen des Gehirns in ihrer Bedeutung für die Hirnlokalisation und Hirnpathologie, in Handb. d. ärztlichen Erfahrungen im Weltkriege, Leipzig, Barth, **4**, 343, 1934.
14. RYLANDER, G.: Personality Changes After Operations on the Frontal Lobes: A Clinical Study of 32 Cases, Acta psychiat. et neurol., Suppl. XX, London, Livingstone, 1939.
15. SCHRADER, P. J., and HOCTOR, E. F.: Bull. State Hosp. No. 4, Farmington, Mo. (tables), 1944.
16. STRECKER, E. A., PALMER, H. D., and GRANT, F. C.: Am. J. Psychiat., **98**, 524, 1942.
17. VAN WAGENEN, R. P.: Personal communication.
18. WALKER, A. E.: The Primate Thalamus, Chicago, Univ. of Chicago Press, 1938.

SCRUB TYPHUS FEVER (TSUTSUGAMUSHI DISEASE) IN NEW GUINEA

REPORT OF 75 CASES

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SCRUB typhus fever today is accepted as identical with Tsutsugamushi disease. It has assumed increasing importance in World War II because of its endemic presence in the Southwest Pacific area and the China-Burma-India theater. The disability and man power loss incurred by it make it a military problem of first rank. Reports gathered from the Southwest Pacific area show a mortality of 2 to 10%. In addition, a very small percentage of those who recover from the severe debilitating form of the disease frequently fail to regain sufficient stamina for general duty even after prolonged periods of convalescence. The minimal time a soldier can be returned to full duty after a moderate attack of scrub typhus fever is 30 to 60 days. In severe cases much longer periods of rest, 3 to 6 months, may be required to recondition the soldier.

Scrub typhus fever is a rickettsial disease caused by *R. orientalis* (*R. tsutsugamushi*). It results from the bite of a larval mite of the genus *Trombicula*, family *Trombididae*, order *Acarina*, and cannot be communicated from man to man. In New Guinea these mites live in areas in which there are large "kunai grass" fields bordering on the jungle. In Japan the mite is called the "kedani mite" and the adult form flourishes along river beds, hence the name "Japanese River Fever." The larval form of the mite, responsible for transmission of the disease, feeds on vertebrates, requiring a blood meal from its host for development to the nymph stage. It becomes infected by feeding on the blood of an infected host. It is said to be able then to pass the disease on to succeeding generations. In New Guinea the rat and bandicoot, of which there are plenty, are the usual hosts; man only accidentally. In Malaya, India, China, Burma, Sumatra and Australia the most

favorable habitat for the mite is the dense thick growth of "scrub" found along small streams in damp jungle common to these regions.

In September 1943 the Surgeon General, because of the increasing problem presented by scrub typhus fever, authorized the sending of an investigating team² to New Guinea. It found that the risk of infection seemed to be associated chiefly with kunai grass fields bordered by jungle along water courses. Such areas offered favorable environmental conditions for the growth and activity of the mite. The investigating team concluded that the risk was maximal during the first 4 to 6 weeks after an organization had occupied a camp site which had not been previously used or cleared, or when an organization engaged in combat was constantly moving into and occupying new areas. Of the cases investigated, 71% became infected within the first days after arrival of the unit in such an area, more than 90% occurred in the first 6 weeks; thereafter the incidence became sporadic. As camp areas were cleared and put in order, the risk of infection became progressively less. This we found to be especially true in this series of cases, as will be pointed out later.

The incubation period varies. There is no absolute information regarding its duration. It is usually stated as being 10 to 18 days, though the maximum period is unknown. In Oda's series of 14 cases, cited by Strong,⁴ whose contacts could be definitely traced, the incubation period varied from 7 to 12 days and averaged 9 days from the time of the bite to the onset of symptoms. On only 1 case of this series was the exact period of incubation computable. One soldier, whose squad had bivouacked on patrol duty in an area from which typhus originated, was relieved and sent to the rear where

MENDELL: SCRUB TYPHUS FEVER

TABLE I.—CLINICAL SUMMARY OF 75 CASES OF SCRUB TYPHUS FEVER

Ill.	Temp.	Pulse	Eschar (location)	Rash	Adenop- athy	Spleno- megaly	Conjunc- tivitis	Epi- staxis	Deaf- ness	System involvement			W.B.C.	Agglutina- tion ONK	Rec.	Died
										Nerv.	Pulm.	C.V.				
1.	103°	90	Axilla	+	+	+	+	+	+	+	+	+	10,000	1:1280	+	
2.	103°	120	Loin	+	+	+	+	+	+	+	+	+	6,400	0	+	+
3.	101°	100	+	+	+	+	+	+	+	+	+	7,000	1:80	+	
4.	101°	86	+	+	+	+	+	+	+	+	+	4,800	1:160	+	
5.	103°	120	Axilla	+	+	+	+	+	+	+	+	+	6,000	N.D.	+	
6.	102°	90	Face	+	+	+	+	+	+	+	+	+	8,000	1:160	+	
7.	103°	84	Scrotum	+	+	+	+	+	+	+	+	+	11,000	N.D.	+	
8.	101°	88	Thigh	+	+	+	+	+	+	+	+	+	9,000	N.D.	+	
9.	103°	92	+	+	+	+	+	+	+	+	+	8,700	N.D.	+	
10.	102°	100	Ankle	+	+	+	+	+	+	+	+	+	N.D.	N.D.	+	
11.	102°	94	+	+	+	+	+	+	+	+	+	6,400	1:160	+	
12.	101°	96	+	+	+	+	+	+	+	+	+	10,200	N.D.	+	
13.	101°	94	+	+	+	+	+	+	+	+	+	6,500	1:160	+	
14.	102°	88	Ankle	+	+	+	+	+	+	+	+	+	4,800	N.D.	+	
15.	103°	94	Leg	+	+	+	+	+	+	+	+	+	5,100	N.D.	+	
16.	101°	88	Knee	+	+	+	+	+	+	+	+	+	6,500	N.D.	+	
17.	101°	96	+	+	+	+	+	+	+	+	+	5,300	N.D.	+	
18.	101°	92	Popliteal space	+	+	+	+	+	+	+	+	+	9,700	1:40	+	
19.	101°	96	Calf	+	+	+	+	+	+	+	+	+	5,100	N.D.	+	
20.	103°	88	+	+	+	+	+	+	+	+	+	8,000	1:80	+	
21.	103°	84	Heel	+	+	+	+	+	+	+	+	+	8,700	1:640	+	
22.	102°	86	+	+	+	+	+	+	+	+	+	3,800	1:80	+	
23.	103°	94	Forearm	+	+	+	+	+	+	+	+	+	7,100	N.D.	+	
24.	101°	96	Thigh	+	+	+	+	+	+	+	+	+	4,300	1:160	+	
25.	103°	101	Sacrum	+	+	+	+	+	+	+	+	+	8,600	N.D.	+	
26.	101°	108	Ankle	+	+	+	+	+	+	+	+	+	6,300	N.D.	+	
27.	101°	96	+	+	+	+	+	+	+	+	+	8,000	N.D.	+	
28.	101°	102	Ankle	+	+	+	+	+	+	+	+	+	8,000	N.D.	+	
29.	101°	108	Arm and thorax	+	+	+	+	+	+	+	+	+	7,000	N.D.	+	
30.	103°	96	Leg	+	+	+	+	+	+	+	+	+	8,300	N.D.	+	
31.	101°	98	Scrotum	+	+	+	+	+	+	+	+	+	7,000	N.D.	+	
32.	101°	90	+	+	+	+	+	+	+	+	+	8,100	1:80	+	
33.	101°	96	Loin	+	+	+	+	+	+	+	+	+	7,800	1:80	+	
34.	103°	100	Axilla and shoulder	+	+	+	+	+	+	+	+	+	11,000	N.D.	+	

there were no typhus mites. He contracted the disease 21 days after exposure. There is no telling how many days prior to leaving the area he had been bitten, hence no standard was available for estimating the time elapsing between the bite and the onset of symptoms. The minute size of the offending mite, the painless nature of the bite, the prevalence of skin affections in the tropics, all tend to make the soldier overlook or place no significance upon the eschar. Frequently, when the lesion was pointed out, he stated he had been unaware of its presence. If he had recognized it, then he had little knowledge of its date of appearance.

Clinical Features of the Disease. The classical picture of scrub typhus fever as was seen here is that of a soldier being stricken suddenly, without warning, with chills and fever, the temperature rising quickly to 103° to 106° F. within 48 hrs. There was invariably a history of exposure to kunai grass in the jungle. Prostration, sweats, malaise, anorexia, joint pains, hyperesthesias, tinnitus soon ensued; occasionally epistaxis, frequently temporary deafness. An eschar, pathognomonic lesion of the disease was usually present from the onset, often requiring careful search of the entire body to disclose. The lymph glands were enlarged and tender, more so in that region of the body draining the eschar. Within 4 to 8 days a macular mulberry rash, non-petechial, appeared over the thorax spreading to the extremities and face, usually subsiding about the 10th to the 12th day. The spleen, always enlarged, was frequently palpable. Leukopenia with relative lymphocytosis was usual, a normal white blood cell count often occurred, leukocytosis was rare unless secondary infection intervened. There was no anemia. In more severe cases, after about 1 wk., nervous, pulmonary and to a lesser extent cardiovascular system involvement appeared. The temperature was continuous early, then became remittent or intermittent, subsiding as a rule by lysis between

the 10th and 20th days. The pulse was slow in proportion to the temperature. The Weil-Felix reaction with OXK strain of *Bacillus proteus* when positive occurred after the 10th day in dilutions of 1:80 or above. It was negative for OX₁₉ and OX₂ strains. In a few cases the agglutination remained persistently negative. The peak of the titer usually occurred during the convalescence. Marked weight loss and asthenia always followed the acute phase of the disease which required long periods of rest and reconditioning before restoration to duty. With the exception of 2 cases, all recovered completely in spite of stormy courses.

Report of 75 Cases Presented. Seventy-five cases have been analyzed and are presented from a series of 87 diagnosed scrub typhus fever over a 3-month period, August-September-October, 1944, while this hospital was stationed in a combat area in north New Guinea where the disease is endemic. Twelve cases have been excluded from this report because they did not absolutely meet the required criteria for a diagnosis, although typhus fever was the most likely explanation of their symptoms. All 12 recovered and were discharged to duty after short periods of convalescence. Of the 75 cases there were 2 deaths, a mortality of 2.7%, which compares favorably with the rate of 2 to 10% quoted for this theater.² In addition, there were 6 cases admitted during this period for post-typhus asthenia in men who had had typhus fever from which they had recovered months previously and had been returned to duty. They were not able to keep up with their fellow soldiers, lacking sufficient stamina, and had to be returned for further periods of rest which finally restored them to full health. These 6 cases serve to emphasize the prolonged convalescence required to rehabilitate the soldier following a severe attack of scrub typhus.

Of the 75 active cases herein reported, 58 occurred during the first 6 weeks of the 3-month period while combat and operations were at their height. During

the next 6-week period, after camp sites had been cleared of grass and scrub, and operations and movements had virtually ceased except for patrol duties, the incidence dropped remarkably, only 17 cases occurring. After that typhus fever disappeared from the admission list. This experience is in keeping with that reported by the Surgeon General's investigating team.

Age is an important factor in the prognosis. As a rule, the younger the individual the less severe the illness, and correspondingly less the mortality rate. It has been shown among civilian populations the mortality rises sharply to as much as 15 to 50% after age 40. One of our 2 deaths occurred in a soldier aged 33 years. Sixty-three of our cases occurred below the age of 30 years, of which 51 were below the age of 25; undoubtedly an important factor in the low mortality rate.

All our patients gave a history of having been exposed to kunai grass in the jungle for periods varying from 2 to 60 days. Fifty-six had slept on the ground in the grass areas, several slept in the scrub during operations and most of the remainder stated they had been on work details cutting, hauling away or burning the grass and scrub.

Fever is a universal finding in this disease. It is rarely under 102° F. and more usual at levels of 104° to 106°. In no case did the temperature endure less than 7 days, the longest was 34 days. Seven cases ranged between 7 and 10 days; 46 (61%) between 10 and 20 days; 18 (24%) between 20 and 30 days; and 4 cases more than 30 days. In 52 cases the temperature reached normal by lysis, in 21 by crisis; 2 died.

The *pulse rates* were slow compared to the temperature curves, 80 to 100 per minute being the usual finding. This is fairly characteristic. Rapidity of the pulse is a guide of oncoming circulatory insufficiency.

The *eschar* is the pathognomonic tell-tale lesion of the disease. Once seen, the

observer will never mistake its presence or significance in the next case. It is so typical that the diagnosis in its presence, with a symptomatology suggesting the disease, can be made regardless of laboratory findings. It appears as a small ulcer, 0.2 to 1 cm. in diameter, circular or oval, resulting from the bite of the larval mite, with a raised reddened areola surrounding it, covered by a black necrotic scar which is shed after a few days leaving a definitely punched out ulcer with a depth of 1 to 2 mm. The mite prefers warm, moist regions of the body, hence selects the axilla, groin, scrotum or belt line to bite. There may be multiple eschars in the same individual.

Fifty-one patients (68%) demonstrated the typical eschar; in 7 eschars were multiple, 6 of whom had 2 and 1 had 3. The majority were located in the axilla, scrotum and groin. In some cases only a careful thorough search of the skin surface yielded the lesion. A small one can be missed easily especially if located in a hidden fold or overlapping fold of skin as occurs in a relaxed scrotum.

The *rash* occurred in most cases between the 4th and 8th days, fading within 2 to 6 days following appearance. It is macular, spoken of as mulberry hue, non-petechial, covers the trunk, extremities and to a lesser extent the face. It was present in 59 cases (78%). Most of the other cases were admitted late and it is possible they demonstrated the rash early which could have been overlooked. In some cases the rash may be so fine that unless the daylight is bright it can be missed. However, this is not usual.

Adenopathy is an almost universal finding. It is usually generalized. Seventy-one patients (95%) demonstrated enlarged, tender lymph glands. The regional glands draining the eschar are always larger and more tender than the others, although the others share in the process. With eschars in the groin, scrotum or lower extremities and the patients lying flat in bed without a pillow, the inguinal glands are often visibly elevated above

the skin level. In severe cases the enlargement may reach the size of a plum. They offer no problem in therapy, never suppurate and subside with recovery.

Splenomegaly occurred in 37 cases. It is a soft, smooth edged spleen not larger than 2 fingerbreadths below the costal margin. While the finding of a palpable spleen is not of too much importance in a malarious area, nevertheless it is always enlarged in scrub typhus fever, whether palpable or not.

Conjunctivitis is a very frequent finding. The intensity of the conjunctivitis usually was proportional to the toxicity and severity of the infection. In many, it was so marked that subconjunctival hemorrhage occurred. It is more an episcleritis originating upon the lid conjunctiva and extending forward over the sclera toward the cornea, decreasing in intensity as it reaches the cornea. There may be accompanying conjunctival separation by edema. Its type is rather peculiar to the disease, is not met with in other diseases with the possible exception of Weil's disease. Fifty-three patients (71%) presented this form of conjunctivitis. All cleared with recovery, leaving no residual signs. One patient who had severe conjunctivitis developed diminished vision in one eye during convalescence, but this was regarded to be due to nerve involvement.

Epistaxis occurred in 9 cases (12%) somewhat less than is usually stated. It offered no therapeutic problem, only 1 patient required packing to control bleeding.

Tinnitus occurred in 36 cases and *deafness* in 26 (35%). The tinnitus was transitory and gave no trouble. The deafness, when present, usually endured throughout the fever period, spontaneously disappearing with normal temperature. While it produced some degree of anxiety in some, most patients were so toxic and apathetic that they were unaware of their decreased auditory powers. In only 1 case did it endure for a 30-day period beyond recovery.

Systemic Involvement. Involvement of the *nervous system* is a frequent finding. When one views the diffuse encephalitis at autopsy, one is surprised that clinical signs of brain involvement do not occur in all cases. Headache, apathy, prostration, hyperesthesias, dizziness occurred in all; tinnitus, deafness, neck pains, tremors, mental confusion and delirium in a large number. Such findings could well be present in any severe septic or toxic state. Therefore, unless definite positive neurologic signs were elicited or convulsions or psychotic manifestations present, clinical nervous system involvement was not diagnosed.

There were 36 patients (48%) with involvement of the central nervous system during the course of their disease. Usually this appeared toward the end of the 1st week and persisted throughout the fever stage. All except 3 made complete recoveries; the 2 who died and 1 who developed a severe post-typhus psychosis for which he had to be evacuated. It was later learned he recovered. There were 2 other patients who developed postinfectious psychosis during the convalescent period; one lasted several days and the other 1 week. Both had to be restrained, but recovery was complete.

Lumbar puncture was required and done in only 1 patient. His headache, neck signs and positive Kernig sign were so severe on admission that meningitis had to be considered. Seventy-one cells, 90% of which were lymphocytes, were found in the spinal fluid. Pleocytosis not infrequently occurs in this disease due to the diffuse encephalitis. Upon recovery of this patient, a second tap disclosed normal findings with 5 cells. No other case required lumbar tap. As a therapeutic measure to relieve pressure, this procedure has not been found of great value by others. We experienced no need for it on this score, and it is felt the patient should be spared any upsetting measures if their value is questionable.

The *lungs* were involved in 38 patients (51%). The more severe the infection,

the more likelihood of the presence of a rickettsial pneumonia or pneumonitis. Ahlm and Lipshutz¹ reported 67% of their cases had atypical pneumonic signs at the height of their illnesses. Every one of our patients manifested cough, chest pain, dyspnea, expectoration at some time during the course of his illness, but unless definite pulmonary signs could be elicited, clinical pulmonary involvement was not diagnosed. Twenty of the 38 patients had a typhus pneumonitis, fairly diffuse, bilateral, manifested by parenchymatous crepitant râles, areas of impairment, limited breathing and altered breath sounds. Eighteen had severe bilateral bronchitis and bronchiolitis characterized by cough, expectoration, occasionally bloody, with rhonchi, sonorous and wheezing râles in the larger and smaller bronchi. The lung signs in all disappeared with recovery except in the 2 cases who died. Roentgen ray film being a critical item in a forward area, routine chest plates were not taken except in 2 instances. One showed a bilateral infiltrative lobular pneumonitis, and the other a similar pneumonitis with a unilateral atelectasis. There is really no need for roentgen ray examination of these patients, and it is better not to disturb them unduly in a disease wherein rest is so vital.

There is no treatment necessary for typhus pneumonia unless secondary infection complicates. Occasionally the cough may be distressing and require sedation. Otherwise the lung findings are reversible to normal with recovery.

Involvement of the *cardiovascular system* occurred in only 3 cases, 2 of whom expired with some degree of congestive failure, the other developing arrhythmia alternating with gallop rhythm during the fever stage. The latter made a complete recovery. In all cases the blood pressure was decreased, hypotension was a constant finding in the sick, prostrated patient. Pressures of 90 to 70 mm. mercury (systolic) and 60 to 40 mm. mercury (diastolic) were usual. Some observers have stated that sodium chloride admin-

istration tended to stabilize the blood pressure level. With recovery, however, the blood pressure returns to normal. Rarely there is some mild peripheral failure associated with the hypotension and generalized vasculitis, but not enough occurred on this series to cause any alarm. In some of the latter instances, plasma was tried but seemed not to affect the situation.

The *peripheral blood picture* is that of a leukopenia with a relative lymphocytosis. Counts of 10,000 were unusual, the highest total count observed was 12,500. A leukocytosis may indicate complicating bacterial infection. Anemia is not associated with the disease. If it be present, another cause should be sought.

The *Weil-Felix* reaction is of great aid in making the diagnosis in doubtful cases. It must be stated, however, that in a small percentage of cases it may remain persistently negative. In most cases there is usually a positive agglutination in titers of 1:160 or more with OXK strain of *Bacillus proteus* and a negative agglutination with the OX₂ and OX₁₉ strains. The degree of positivity with OXK is by no means proportional to the severity of the disease. Three of our sickest patients had zero agglutination throughout their illnesses and convalescence; 1 death had a zero agglutination, and the other only 1:80. Some writers have explained such low titers in fatal cases as a failure of the body forces to manufacture antibodies. This is not an established fact, however. The mildest case, with fever for only 7 days, had an agglutination of 1:60.

In this series, the clinical findings were correlated in every case with the titer of the agglutination. While others speak of 1:160 or above as being a positive Weil-Felix for OXK, still others have found 1:80 significant especially if demonstrated in rising titer. The titers of 1:80 or higher among our patients were the result of several tests performed a week apart after the 2nd or 3rd week of illness. The original reaction was usually negative or lower in titer. In many of the lower

titers obtained, the presence of the eschar or classical clinical features of the disease, or both, rendered the diagnosis undoubted in spite of the low Weil-Felix agglutination. In the report of Ahlm and Lipshutz, of 57 agglutinations performed, 21 were negative or 1:80 or less in proven cases of scrub typhus.

As we were stationed in a forward area of combat, our supply of antigen was limited and soon ran out. It was decided, therefore, not to do the test in cases with eschars in which the diagnosis was evident, but only in cases in which the diagnosis was in doubt and wherein the clinical findings were not conclusive. Many cases fell into the latter group, demonstrated negative agglutinations and do not appear in this report. In that sense the negative agglutination proved of value in eliminating the diagnosis. Later in this study, we received a small replacement supply of antigen and were able to be a bit more liberal in performing the Weil-Felix test.

The agglutination test was performed in 34 patients of this series, in many at least twice to demonstrate rising titers. Eight patients had titers of 1:40, of whom 7 had eschars and all 8 demonstrated the clinical features of the disease. Twenty-three patients had agglutinations of 1:80 or above, of whom 12 had eschars, and in all 23 the diagnosis was beyond question. Three patients, 1 of whom died, with typical eschars and clinical symptomatology had zero agglutinations. It is worth repeating, that whereas a positive agglutination of 1:160 or more with OXK strain of *B. proteus* is very valuable in establishing the diagnosis, the disease picture is so definite, rendering itself so readily to diagnosis in areas wherein it is endemic, that an agglutination is not absolutely necessary to the clinician except in doubtful cases. Therefore, for an Army Hospital in the field not equipped to do such a laboratory procedure because of lack of supplies or trained personnel, diagnostic accuracy should not be seriously handicapped.

Isolation of the rickettsia from the patient's blood was not attempted. However, this procedure is easy of performance and can be of great value.

The *pathologic anatomy* of scrub typhus fever is that of a vasculitis and perivasculitis of the smaller vessels involving chiefly the reticulo-endothelial system, brain, lungs and heart. The picture is best presented by the following two autopsies performed upon the 2 patients who died.

CASE 1. Male, white, age 23, infantryman, was admitted to this hospital on Aug. 14, 1944, with a diagnosis of dengue. His illness began suddenly on August 6, with chills and quickly mounting temperature to 104° F. daily. The diagnosis was changed to scrub typhus fever on August 16. He had served in a combat operation in the jungle, had slept on the ground in the kunai grass area, but had no knowledge of having been bitten by a mite or other insect. He complained of profuse sweats, headaches, dizziness, malaise, joint pains, anorexia, tinnitus and deafness. He had generalized aches and was exquisitely tender over his limbs. No eschar was found, but adenopathy was generalized and the glands were tender and soft. Conjunctivitis was marked. He soon developed circumoral twitchings, mental confusion, and delirium. Nuchal rigidity and bilateral positive Kernig signs were present; the last 2 days before death he developed generalized convulsions. The lungs exhibited a diffuse, bilateral pneumonitis. Blood pressure range averaged 80/60 mm. of mercury. The temperature ranged between 100° in the morning to 105° and 106° in the evening. The leukocytes were 6700 and relative lymphocytosis was present. Weil-Felix reaction with OXK was 1:80, negative with OX₂ and OX₁₉. He died on August 21, 15 days after onset of illness.

Clinical Diagnosis. Scrub typhus fever with terminal cerebral involvement.

Postmortem Examination (Capt. Henry Brody, M.C.). Body is that of a white male, 167 cm. long, estimated weight 135 lbs. Conjunctivæ are injected and slightly chemotic. Right axillary lymph nodes are enlarged, those in left axilla palpable. Scattered over trunk both anteriorly and posteriorly and extending to a lesser extent to the neck and upper portions of the lower

extremities, are innumerable vesicles varying in size from a pin head to almost 5 mm. in diameter. The fluid in all but one of the vesicles is clear, that on smear yielded staphylococci. Small shotty lymph nodes are present in both inguinal regions. Careful examination of the entire external aspect of the body reveals no ulcerated lesion or eschar.

The panniculus is scant. The muscles of chest and abdominal walls are exceedingly dry and a deep red. Abdominal organs are normally disposed, and peritoneal surfaces smooth and glistening. The liver edge is 3.5 cm. below the xiphoid in the midline. The spleen is enlarged but entirely within the costal border. The domes of the diaphragm are at a level of the 4th rib on the right and the 6th on the left. The thymus is small, the pleural cavities contain no fluid. Adhesions are present at the right apex. The pericardial cavity contains about 30 cc. of clear yellow fluid.

The heart is of normal size and shape. The ventricular cavities are slightly dilated, the myocardium is slightly flabby. On incision, the myocardium shows a faint mottling, with yellow brown and brownish red areas alternating. No scars or focal lesions seen. The endocardium is smooth throughout. The valves appear normal. Except for a single tiny atheromatous plaque close to the mouth of the left coronary artery, the coronary arteries are not remarkable.

The lungs are voluminous. On the right adhesions bind the pleura to the parietes. A small amount of fibrin is loosely adherent to the pleura at several points. Otherwise, the pleura is smooth and glistening. The dependent portions of both lungs are deep purple as contrasted with the light pink of the upper portions. The dependent portions are boggy but without areas of consolidation. On section these portions are deep purple, moderately wet, with a small amount of bloody fluid pouring from the surface. The upper lobes show some areas of slight congestion, but for the most part are pink and air containing. Anthracotic markings are minimal. No pneumonia is recognized. The bronchial mucosa is hyperemic, and a few of the larger ones contain a little frothy fluid which is blood tinged. The pulmonary vessels show nothing unusual. Their endothelial lining, as far as could be traced, shows no gross visible damage. The hilar

and mediastinal lymph nodes are not appreciably enlarged.

The spleen is between 3 and 4 times normal size, estimated to weigh about 350 gm., measuring 16 x 11 x 9 cm. The capsule is smooth and tense. On section, the Malpighian bodies, which are small, stand out clearly against the soft, deep purple pulp. The pulp can be scraped away with a knife. No pigmentation, infarcts or necrosis are seen.

The right kidney measures 19 x 7.5 x 4 cm., the left 14 x 8 x 5.5 cm. Their capsules strip with ease, leaving a smooth surface. The cut surface shows normal markings. The calyces and pelves are normal. Both renal arteries and ureters are normal. The suprarenals are small and thin, on section they appear rather poor of lipid content. The urinary bladder is distended with urine, the epithelial surface is pale, there are no diverticulæ. The trigone is not remarkable. The prostate is small. The seminal vesicles, epididymes and tests all appear normal.

In the lower third of the esophagus, a small bleb, similar to those seen on the skin, is found. The stomach and intestinal tract are not remarkable. The mesenteric lymph nodes are slightly enlarged. The liver appears larger than normal, measuring 29 x 19 x 10 cm. The capsule is smooth, the cut surface shows slight congestion with fine, distinct architectural marking. The gall-bladder contains 25 cc. of thick brownish green bile. The cystic, hepatic and common ducts are normal. A lymph node measuring 3 x 1.5 x 0.5 cm. is present close to the Heisterian valve. The pancreas is normal. The thyroid is small, its cut surface pale and glossy. The blood-vessels show practically no atherosclerosis, as is also true of the larger branches. The venous and portal systems are normal.

The brain appears large and there is some slight increase in subarachnoid fluid. The pial vessels are slightly engorged. No hemorrhages, petechiæ or areas of exudate are found. On section, after fixation, many of the pial vessels are distended with firm clot. Similarly, small vessels throughout the substance of the brain are distended. No striking anatomic distribution is recognized, though they are somewhat more numerous in the basal ganglia, bilaterally, than elsewhere. The ventricles are not dis-

tended. No areas of necrosis or hemorrhage are found.

Histologic Study (Capt. Emmett B. Settle, M.C.). The heart sections show characteristic acute focal and diffuse myocarditis. Acute serous pericarditis is also present. Sections of the aorta show minimal perivascular mononuclear infiltration about the vasa vasorum. The lung sections show characteristic acute primary interstitial pneumonia with vascular inflammation and damage, hemorrhage and acute congestion with edema. Other sections show an acute secondary bronchiolitis with acute secondary lobular bronchopneumonia. An acute serous pleuritis is present. The spleen shows characteristic acute splenitis with congestion and hemorrhage. The lymph node sections show characteristic acute adenitis with congestion, hemorrhage and focal necrosis. The stomach is essentially normal, there is a mild vasculitis and perivasculitis. The adrenal sections show interstitial clumps of mononuclear cells of the medulla and vascular zones. The kidney sections show characteristic acute focal interstitial nephritis with mononuclear infiltration. The renal tubular epithelium shows cloudy swelling. Sections of the testicles show mild perivascular mononuclear infiltration with interstitial edema. Physiologic stage of involution is seen in the thyroid. Sections of the skin show mild perivascular mononuclear infiltration about the capillary loops of the papillary bodies as well as the deep and superficial network of the corium. Sections of the brain show vasculitis and perivasculitis with an occasional nodule and punctate hemorrhage. Some sections show a mild serous leptomeningitis. The liver specimen was not received.

Pathologic Diagnosis. 1. General: (a) Tsutsugamushi disease (scrub typhus).

2. Cardiovascular System: (a) Vasculitis and perivasculitis, acute generalized, minimal to moderate. (b) Myocarditis, acute focal and diffuse, mild. (c) Pericarditis, acute serous mild.

3. Respiratory System: (a) Pneumonia, acute primary interstitial, severe. (b) Pleuritis, acute, serous, mild. (c) Bronchopneumonia, acute, lobular, secondary, mild. (d) Bronchiolitis, acute, purulent, mild.

4. Spleen and Hematopoietic Tissues: (a) Splenitis, acute with congestion, hemorrhage and splenomegaly. (b) Lymphaden-

itis, acute, with congestion, hemorrhage, focal necrosis and lymphadenopathy.

5. Gastro-intestinal Tract: Normal.

6. Genito-urinary System: (a) Nephritis, acute, focal, interstitial, mild. (b) Cloudy swelling of renal tubular epithelium. (c) Orchitis, acute interstitial, mild.

7. Central Nervous System: (a) Encephalitis, acute focal, mild, with congestion, edema and focal hemorrhage. (b) Leptomeningitis, acute serous, minimal.

CASE 2. Male, white, age 33, infantryman, was admitted on Oct. 22, 1944, for cough, soreness in chest, chills, vomiting and temperature of 104° F. His illness began 7 days previously with fever, sudden in onset. He had been on advance patrol duty which took him far into the jungle, where he had been exposed to kunai grass and scrub for several weeks. He was extremely toxic; there was a scattered erythematous macular rash present over back, arms and shoulders. An eschar 1 cm. in diameter with a black necrotic covering was present over the right postero-lateral lumbar area. The lymph glands were all enlarged and tender, more so in the inguinal regions. The spleen could not be felt. Conjunctivitis with subconjunctival hemorrhages were intense. There was a bilateral extensive lobular pneumonitis, nuchal rigidity, positive Kernig, tremors and mental confusion. The course was rapidly downhill, toxicity and prostration were profound, temperature remained between 104° and 106° F. daily, blood pressure 58/40. On the 12th day of the disease the Weil-Felix reaction with OXK was zero. The leukocytes were 6400 with 52% lymphocytes. On the 13th day, oliguria appeared which developed into complete anuria, the non-protein nitrogen rose to 100 mg. per 100 cc. On the same day, acute congestive cardiac failure appeared which was quickly digitalized. He expired on Oct. 30, 1944, the 15th day of his illness.

Clinical Diagnosis. Scrub typhus fever.

Postmortem Examination (Capt. Henry Brody, M.C.). The body is that of a well-developed white male, estimated weight 160 lbs. There are extensive subconjunctival hemorrhages bilaterally. Between the mid and posterior axillary lines, above the crest of the ilium, there is a partly healed eschar. The crust has dropped off, the base is yellow and granular, the edges are sharp, the ulcer base is 1.5 mm. below the skin surface. The

skin immediately around the ulcer appears slightly indurated and hyperemic. Otherwise the external appearance of the body is not remarkable.

The liver edge is at the costal border. The spleen, though enlarged, is within the costal border. The thymus is small. There are about 50 cc. of clear fluid in each pleural cavity. The abdominal organs are normally disposed.

The heart: The pericardial cavity contains 15 cc. of fluid; pericardial surfaces are smooth. The right ventricle appears dilated, otherwise shows no abnormalities. The endocardium of the left atrium, immediately above the posterior leaflet of the mitral valve, appears wrinkled and somewhat orange yellow. The chordæ tendineæ of the mitral valve are thickened. Along the line of closure of the anterior leaflet there is a thickened fibrous ridge about 2 mm. in thickness and 1.5 cm. in length. The valve does not appear deformed and was undoubtedly functionally sufficient. In the left ventricle there are several patches of endocardial thickening, light yellow in appearance. The largest of these involves the base of the anterior papillary muscle. The thickened portion of the endocardium is light yellow. The left ventricle is neither dilated nor hypertrophied. The aortic valve shows nothing remarkable. The coronary ostia are normal. The coronary arteries show some atheromatous streaking, but no serious impairment of their lumen. The aorta is elastic with moderate atheromatous streaking.

In the lungs, old fibrous adhesions are found between the lobes bilaterally. Pleural surfaces are smooth and glistening, except for an area about 10 cm. in diameter on the lateral aspect of the right lower lobe, where it is a dull purple. The surface at this site has lost its sheen. The upper lobes bilaterally are partly crepitant, the lower lobes have a somewhat rubbery consistency. A number of tiny fibrous anthracotic nodules are scattered throughout both lungs. The lower lobes appear somewhat atelectatic. On palpation there are scattered small areas which feel firmer than elsewhere. The general surface on section is dull purple, and tiny areas perhaps slightly more gray and drier appear throughout. The larger bronchi contain blood streaked mucus. The pulmonary vessels are normal. The hilar lymph nodes

are enlarged and soft. No calcific or caseous nodes are found.

The spleen is about 3 times normal size. The capsule is smooth, there is a spleniculus. On section, the pulp is firm and deep purple. The Malpighian bodies are very prominent and numerous, larger than normal. The splenic vessels are normal.

The kidneys appear slightly large, the capsule is tense but strips easily leaving smooth surfaces. The cortex appears very pale and light gray. The glomeruli can scarcely be made out. The outer 2 or 3 mm. of each pyramid is deeply engorged. This forms a symmetrical pattern throughout both kidneys. The central portion of each pyramid and the renal papillæ are unusually pale, somewhat glassy in appearance. This hyperemic scalloping, separating the cortex from the central portions of each pyramid, makes a striking picture. The renal pelves show subepithelial hemorrhages. The ureters are normal. The urinary bladder is collapsed, its epithelium pale. There are only a few cc. of urine in the bladder. The trigone is normal, prostate small. The seminal vesicles contain rather viscid brown fluid. The epididymes and testes are normal.

The liver is normal in size, capsule is smooth, architectural pattern preserved. There is no gross evidence of fatty change. The gall bladder is distended with viscid green bile, the duct system is normal. The pancreas is not remarkable. The gastrointestinal tract is normal except for slightly enlarged mesenteric glands.

The iliopsoas muscle on the right side is the seat of extensive hemorrhage. It is friable. No similar lesion is seen in any of the other muscles.

The brain was not removed.

Histologic Study (Capt. Herbert J. Levin, M.C.). The heart shows an arteriolitis and periarteriolitis with marked narrowing of the vessel lumina due to endothelial hyperplasia. There are numerous small areas of hemorrhage, principally perivascular and the myocardium shows profound cloudy swelling, fragmentation and hyaline necrosis. In some areas there is advanced fatty replacement. Another section shows massive subepicardial hemorrhage. In a section of a cardiac leaflet there is marked vascularized fibrous thickening but no evidence of recent inflammation. Sections of the aorta show advanced

vasculitis and perivasculitis of the vasa vasorum.

The lungs show numerous heart failure cells in the alveoli. The alveolar septa are thickened due to accumulations of small and large mononuclear cells. Few of the blood-vessels show intimal hyperplasia.

The spleen sections show pulp hyperplasia with considerable blood pigment present in the endothelial cells. The splenic corpuscles are atrophic. They show hyperplasia and hyalin necrosis of the germinal centers. Lymph node sections show only endothelial hyperplasia and anthracosis. The liver sections show marked vasculitis and perivasculitis of the interlobular vessels. There are prominent small cell aggregates in the periportal spaces. Old blood pigment is found in the periphery of the liver lobules. The pancreas shows chronic inflammatory cell infiltration and fibrosis of the interstitial connective tissue.

The kidney sections show a pronounced vasculitis and perivasculitis. Blood-vessels in the medulla are greatly dilated and packed with red cells. The proximal convoluted tubules are dilated, swollen and tufted; in their lumina is granular debris. There is a prominent lymphocytic invasion of the interstitial tissue and there are occasional delicate adhesions between the congested glomeruli and the Bowman capsules. The adrenals, testes and prostate present no pathologic changes.

Pathologic Diagnosis. 1. General: Tsutsugamushi disease (scrub typhus type), acute, severe.

2. Cardiovascular System: (a) Vasculitis and perivasculitis. (b) Hemorrhages multiple. (c) Myocardial cloudy swelling and hyaline necrosis. (d) Fatty changes. (e) Endocarditis, rheumatic, mitral, old, healed. (f) Pericardial effusion.

3. Respiratory System: (a) Vasculitis, minimal. (b) Interstitial pneumonitis. (c) Congestion. (d) Pleural adhesions, bilateral.

4. Spleen: Hyperplasia, marked.

5. Liver. Vasculitis and perivasculitis.

6. Kidneys: (a) Vasculitis and perivasculitis. (b) Interstitial nephritis.

7. Pancreas: Interstitial pancreatitis.

8. Muscle: Hemorrhage, massive, iliopsoas, right.

9. Miscellaneous: (a) Hemorrhages, subconjunctival. (b) Ulcer, of skin, healing, right posterior lumbar region.

Epicrisis. Cause of death in this case was an uncomplicated typhus infection with most marked changes in the heart muscle.

Treatment. There is no specific treatment for scrub typhus fever. Good nursing care, absolute rest which includes the avoidance of measures which will disturb the patient, maintenance of nourishment, fluids, salt and vitamin intake form the backbone of any successful management. The treatment as recommended in War Department Technical Bulletin (Med. 31)³ is based on a large accumulated experience with scrub typhus and is sound and well worth applying. One must be cautioned against the temptation to over-treat these patients; excessive symptomatic treatment should be discouraged.

Penicillin and the sulfonamides are without value unless secondary infection complicates. Indeed, sulfa drugs may prove harmful. The daily administration of 6 gm. of salt is important, a hypochloremia has been demonstrated in the fever stage. Salt may be given orally, or by slow intravenous drip as normal physiologic saline; 3000 cc. of fluid should be given per day, orally and parenterally. As long as intravenous infusions are given slowly, the circulatory system is unaffected. Digitalis is of no value except in acute congestive cardiac failure. Plasma is not needed unless hypoproteinemia with edema occur, which we did not experience in our patients. Some have utilized plasma as a measure to maintain blood pressure; we tried it but failed to note any effect. Oxygen therapy proved of little value in the pneumonia seen in the disease, but of more value in complicating congestive heart failure. 2500 to 3500 calories per day is a necessary factor for the patient; however, few are disposed to eat during the acute stage and must be constantly urged. The eschar requires no treatment other than a sterile, dry dressing; it heals spontaneously within a few weeks leaving a scar of no moment. The pneumonitis requires no special treatment other than a sedative for cough

now and then; the meningeal manifestations likewise require no special measures; both reverse to normal with recovery. This is also true of the hypotension. Cardiac failure requires prompt digitalization. The conjunctivitis may occasionally require a mild astringent, otherwise, even if severe, is best left alone. The deafness is temporary and should be handled only with reassurance.

The *convalescence*, once recovery stage is reached, assumes a most important rôle in restoration of the individual. Rest periods varying from 1 month in mild cases to 6 months in very severe infections may be required to counteract the prostration, asthenia, weight loss and reverse the pathology characteristic of this disease. Occasionally it becomes difficult to estimate when a soldier is fit to return to duty following this infection, as is illustrated by the 6 patients who required readmission for longer periods of rest. In all instances they were ultimately returned to full health and duty.

The attendant should never underestimate the value of reassurance in these patients. Anxiety states develop easily and erroneous ideas about the disease are current among them. Typhus fever is a dreaded infection among troops; since there are no "shots" to prevent it, they feel it is fatal; or if a victim should be fortunate enough to survive, that he will be left a cardiac invalid for the remainder of his life. Reassurance will go far to relieve such patients and prevent a disabling neurosis after recovery.

Study of a large series of convalescent typhus cases reported by the Chief Surgeon, United States Army Forces in the Far East⁵ in which physical signs, roentgen findings, electrocardiograms, vital capacities and exercise tolerance tests were performed, demonstrated the absence of involvement of the cardiovascular system following recovery. Functional neurocirculatory symptoms were found to be not more frequent than encountered in any other severe febrile state.

Without a specific curative treatment,

the *prophylaxis* and prevention of the disease assume a very important rôle. There is no vaccine to date for general use which will actively immunize troops going into infected areas. The clearing of camp sites of scrub and grass, wearing full uniform to cover the body, frequent bathing, impregnation of clothing with repellents for mites (of which dimethyl phthallates are most effective, avoidance of sleeping on the ground) are all measures, which if possible to employ will reduce the rate to a minimum even in a heavily infected area. If the military situation permits the camp site or bivouac area to be carefully chosen away from scrub, grass, jungle or streams, much of the problem will be obviated. If military operations require bodies of troops in mite infested areas, rigid prophylactic discipline as recommended in War Department Technical Bulletin (Med. 31) will go far to wipe out the disease.

Discussion. Before the advent of World War II, scrub typhus fever or tsutsumushi disease was a rare medical curiosity to the American physician. With the war and the transportation of large numbers of American troops to the Southwest Pacific and Far East theaters, the disease became a problem of paramount importance to the war effort, and to those of us engaged in caring for the health of these troops. For most of us, this was our first experience with scrub typhus fever. American texts offered only meager descriptions and discussions, and references upon the condition were not as numerous as one would like.

Following the war, it is more than likely that armies of occupation as well as civilians endeavoring to develop hitherto untouched resources in these lands will have to cope with the problem of scrub typhus. The large number of cases available for study among troops offers an excellent opportunity to accumulate more knowledge about the disease.

The etiology, transmission, clinical features, pathology and nature of scrub typhus are well established and under-

stood. The isolation of the rickettsia from the patient's blood stream and the Weil-Felix agglutination with OXK in titers of 1:160 or more are conclusive evidences of the disease. A negative agglutination, however, does not eliminate the diagnosis. The clinical features, namely the eschar, fever course, rash, adenopathy, splenomegaly, conjunctivitis, temporary deafness, with involvement of the brain, heart and lungs, are so characteristic that recognition of the disease, even in the absence of laboratory findings, is fairly simple. The need for laboratory confirmation assumes more importance in the doubtful cases.

In general, it may be said that all tropical diseases prevail because of inadequate sanitation. The incidence of these diseases is inversely proportional to the degree of sanitary measures employed. The American Army with its high sanitary standards has done a remarkable job in the midst of difficult war conditions, of reducing the occurrence and mortality of tropical diseases. Its methods and principles could serve as a basis for governmental projects after the war to eliminate the hazards of these infections wherever man may be obliged to go. The findings of the Surgeon General's investigating team in New Guinea, which our experience corroborated, have shown that scrub typhus can be reduced to a minimum even in heavily infected areas. After the war, it could be totally eliminated, if the knowledge we already possess is applied.

Thanks is acknowledged to Capt. H. H. Schlomovitz, William B. Miller, Paul D. Shore and Philip H. Prose, M.C., A.U.S., whose detailed ward records permitted this analysis.

REFERENCES

1. AHLIN, C. E., and LIPSHUTZ, J.: Tsutsugamushi Fever in the Southwest Pacific Theatre, *J. Am. Med. Assn.*, 124, 1095, 1944.
2. Scrub Typhus, *Bull. U. S. Med. Dept.*, No. 76, May, 1944.
3. Scrub Typhus Fever (Tsutsugamushi Disease), *War Dept. Tech. Bull. Med.* No. 31, April 11, 1944.
4. STRONG, R. P.: *Stitt's Diagnosis, Treatment and Prevention of Tropical Diseases*, 6th ed., Philadelphia, Blakiston.
5. Treatment and Disposition of Patients Convalescing From Scrub Typhus, *Hqs. U. S. A. Forces in the Far East, Off. of Chief Surgeon, Tech. Memo.*, No. 10, Aug. 29, 1944.

Until a specific vaccine is developed, or a better treatment devised to reduce the morbidity and mortality, the prophylaxis and employment of sanitary measures to prevent the disease offer the most hope for its eradication. These procedures have been so well laid down by the War Department, already referred to in this report, that their institution under the most rigid discipline is urged to keep the disease under control.

Summary and Conclusions. 1. Scrub typhus fever (Tsutsugamushi disease) as seen in a Station Hospital in north New Guinea during a combat period in which our troops were exposed to the disease, is reported.

2. In an analysis of 75 cases, 2 died, 73 recovered. The mortality of 2.7% is low for this serious infection.

3. The etiology, transmission, clinical features, laboratory findings, treatment and prevention are discussed.

4. The characteristic pathologic changes (a vasculitis and perivasculitis of the smaller vessels involving chiefly the heart, lungs, nervous system and reticulo-endothelial tissues) are well illustrated in the 2 autopsies presented.

5. With the knowledge at our disposal today, the institution of adequate sanitation and prevention measures, the disease could be eliminated in all areas where white man may travel after the war.

6. The record of the American Army in the reduction of the mortality and morbidity of this disease among our troops is to be commended.

THE CLINICAL SIGNIFICANCE OF COLD HEMAGGLUTININS

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FROM the clinical standpoint, cold hemagglutinins are considered important chiefly (1) because their appearance during the course of pulmonary infections may aid in the diagnosis of primary atypical pneumonia, and (2) because their development from whatever stimulus may be followed by vascular occlusion and rapid destruction of erythrocytes.

The literature pertaining to cold hemagglutinins have been reviewed recently by Stats and Wassermann.⁴² It is, therefore, necessary only to point out that these agglutinins were thought to be of relatively little consequence until 1943 when Peterson, Ham and Finland³⁵ made the important discovery of their association with atypical pneumonia. The immunologic properties of cold agglutinins had been presented in detail by Clough and Richter³ in 1918 and by Wheeler, Gallagher and Stuart⁴⁵ in 1939. In retrospect the 2 cases presented by these authors might well be labeled "primary atypical pneumonia." However, the relationship between the pneumonitis and the presence of these peculiar antibodies was not recognized at the time of their observations. Although numerous brief reports concerning cold agglutinins in atypical pneumonia have appeared since the early months of 1943, many questions remain incompletely answered. The investigations reported in this paper were, therefore, undertaken with the following objectives:

1. To study certain technical factors affecting the results of tests for the presence of cold hemagglutinins in human serum, and thereby to propose a suitable test for routine hospital use.

2. To study the development of cold hemagglutinins in primary atypical pneumonia with special reference to (a) the incidence of titers above the range commonly encountered in other diseases and in normal individuals, (b) the time of their appearance and disappearance, (c) the relationship between titer and severity of illness, and (d) their diagnostic value.

3. To determine the extent to which cold hemagglutinins develop in diseases other than atypical pneumonia, particularly in other respiratory infections and in diseases associated with splenomegaly.

4. To determine whether or not cold agglutinins found in association with various disorders have any distinctive immunologic properties which might aid in differential diagnosis.

5. To make special note of any hemolytic or vascular complications that might be attributed to the presence of cold hemagglutinins.

Methods. Blood was collected in sterile, corked tubes, and the serum was separated by centrifugation after the blood had stood at room temperature for several hours. Any specimens that had inadvertently been placed in the refrigerator were warmed in an incubator at 37° C. for 1 hr. before being placed in the centrifuge.

In the majority of instances the first tests of the sera were made within 1 wk. after the blood was drawn, and nearly always within 2 wks. For purposes of storage, all sera were kept in sterile Wassermann tubes tightly closed with rubber stoppers and sealed with paraffin. All tubes were stored at 4° C. in wire racks appropriately labeled and arranged for ready use. A card index file facilitated the cataloguing of specimens.

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Presumptive Tests. After a sufficient number of sera had accumulated, presumptive tests were carried out by placing 0.1 ml. of each specimen (without inactivation) in the bottom of a 10 x 75 mm. tube. To each tube 0.3 ml. of a 0.67% suspension of Group O human red blood cells in physiologic saline solution was added. The tubes were then shaken and placed in the refrigerator overnight at 4° C. The following morning the tubes were examined grossly for the presence or absence of agglutination. Those showing no clumping of the red cells were designated as negative and were not ordinarily retested; those showing \pm agglutination were recorded as positive in a 1:4 dilution of serum and were likewise not ordinarily retested.

Titration of Serum. Sera giving stronger reactions were titrated as follows:

Result of presumptive test	Range of dilutions set up in titration
+	1:4 to 1:32
++	1:4 to 1:128
+++	1:4 to 1:256
++++	1:4 to 1:1024 (or higher)

Serial 2-fold dilutions of serum were made with saline in 10 x 75 mm. tubes. To 0.5 ml. of each dilution was added an equal volume of a 1% suspension of Group O human red cells. The tubes were then shaken, placed in a refrigerator at 4° C. overnight and examined grossly the following morning. The racks were removed from the refrigerator 1 at a time and if there was any delay in the examination, they were placed in a shallow pan of cracked ice in order to maintain the temperature as near 4° C. as possible.

Each tube was held in a nearly horizontal position and gently shaken (usually 3 to 5 times) until all cells in the bottom had been dislodged. The cell suspension was then carefully scrutinized over a well-illuminated white background and the last tube showing grossly detectable agglutination was taken as the end-point. Titers were recorded in terms of the final dilution of serum after addition of cell suspension. That is, the first tube containing 0.25 ml. serum + 0.25 ml. saline + 0.5 ml. cell suspension was regarded as having a 1:4 dilution. Reversibility of the agglutination was checked by examining the tubes after standing at room or incubator temperature for 1 or more hours.

Preparation of Cell Suspensions. Nearly all of the tests recorded in this paper were made with Group O red cells from 1 of 3 normal individuals. Approximately 5 ml. of blood were mixed with 1 ml. of 3.8% sodium citrate. The plasma was removed after centrifugation and the cells washed 3 times with saline, after which 0.67% suspensions in saline were prepared for presumptive tests and 1% suspensions for titrations. After mixing with serum, the final concentration of cells in each tube was 0.5%. Blood was not used after 24 hrs. and all cells were washed immediately before use. The variation in sensitivity of cells from different sources will be discussed later.

Investigation of Factors Affecting the Results of Tests for Cold Hemagglutinins.

Storage of Serum. The rate at which demonstrable antibodies disappear from serum on storage is often an important consideration in serologic studies. The reports of Peterson, Ham and Finland,³⁵ and Horstmann and Tatlock¹⁹ indicate that cold hemagglutinins are less apt to be present in high titer in sera stored 1 to 14 mos., and Favour⁹ emphasizes the decrease in titer that may occur during the first 3 wks. of storage, especially if the serum is repeatedly warmed for sampling. McNeil,³¹ on the other hand, found that titers were maintained during the first 6 weeks of storage but decreased markedly during the 2nd period of 6 weeks.

During the course of the present study 20 sera from 13 patients with atypical pneumonia were tested soon after collection (average interval 4 days) and again with identical technique after 2 to 10 mos. of storage at 4° C. without preservative. In each instance the suspension of red cells used in the second test was prepared either from the same donor used in the first test or from another donor whose cells had been shown to have approximately the same degree of sensitivity. Variations of 1 tube in either direction are considered insignificant. The results are shown in Table 1 and indicate that although considerable loss of potency may occur with storage, this is by no means the rule. Nevertheless it is clear that sera should be tested soon after collection if possible.

Use of Presumptive Test. The task of examining many sera at the same time can be greatly simplified by employing the

1-tube presumptive test already described. The final dilution of serum in the single tube of the presumptive test might be adjusted to 1:10 rather than 1:4, since titers less than 1:10 are of no significance. Use of the presumptive test was adopted after repeated examinations of many sera for cold hemagglutinins failed to disclose any prozone phenomena.

TABLE 1.—CHANGES IN TITER OF 20 SERA FROM 13 PATIENTS WITH ATYPICAL PNEUMONIA AFTER 2 TO 10 MONTHS' STORAGE AT 4° C

Number sera showing no significant change				Number sera showing significant decrease in titer			
Same	1 tube lower	1 tube higher	Total	2 tubes lower	3 tubes lower	4 tubes lower	Total
6	5	4	15	1	3	1	5
Average storage: 213 days				Average storage: 153 days			

There is no advantage in using the presumptive test if a single specimen of serum is to be examined.

Choice of Red Blood Cells. The studies of Landsteiner and Witt,²⁶ Kettel,^{22,23,29} and Stats and Wasserman⁴² indicate that there is considerable variation in the sensitivity of red blood cells from individuals representing the various blood groups and subgroups. Kettel obtained lowest titers with autologous cells and highest titers with other erythrocytes of the same blood group. Humphrey,²⁰ on the other hand, found autologous cells far more sensitive than Group O cells.

Tests for cold hemagglutinins are ordinarily carried out by using either autologous cells from the patient or Group O cells from a convenient donor. The need for determining the degree of variation in sensitivity of erythrocytes from these sources is obvious. With this objective in mind, the following experiments were undertaken.

Relative Sensitivity of Group O Cells From Various Sources. Ten sera from 9 patients were titrated with fresh cells from 5 different Group O donors, including A. R., the donor who furnished cells for about 45% of the tests reported in this paper. The 10 sera were selected to include a wide range of potency. The titrations were set up in the usual way and the degree of agglutination in each

tube was recorded. The results obtained with 5 of the 10 representative sera, as shown in Table 2, indicate clearly that the cells from donor A. R. are more sensitive than the others. However, the greater sensitivity of these cells is apparent only in titrations of relatively weak sera. When more potent sera (M. W. and J. D.) were tested, differences in sensitivity of

cells from various sources were not readily demonstrable.

Titration of the 10 sera with cells from the same 5 Group O donors was repeated after the cells had been stored (with plasma, under sterile conditions) in the refrigerator for 3 days. The reactions were slightly weaker with the 3 day old cells but again the greater sensitivity of A. R.'s cells was apparent in the test with weak sera.

In the second experiment of this type, 31 specimens of serum from 30 patients were titrated with cells from donors A. R. and W. V., the donors whose cells had previously shown greatest and least sensitivity respectively. These sera were selected because they had given relatively low titers in preliminary tests. Twenty-six of the specimens gave significantly stronger reactions and higher titers with A. R.'s cells, 1 showed equal potency with cells from the 2 donors, and 4 of the sera agglutinated W. V.'s cells more strongly than A. R.'s. Unfortunately these titrations could not be repeated, but nevertheless the greater sensitivity of A. R.'s cells was apparent in tests with most of the sera, particularly the weaker specimens.

Cells from donor R. J., who had provided blood for about 50% of the titrations recorded in this paper, became available for study on Aug. 28, 1944. Eight

sera from 8 patients were titrated with cells from R. J. and A. R. with nearly identical results. A. R.'s cells showed only slightly greater sensitivity. For practical purposes it can be said that the cells of R. J. and A. R., which were used in about 95% of the tests included in the clinical study, were of nearly equal sensitivity and were the most sensitive of all cells tested. Most of the remaining 5% of the tests were carried out with cells from donor R. S. (see Table 2). The sensitivity of these cells was intermediate between that of A. R. and W. V. Detailed presentation of the above results is omitted to conserve space.

pensions prepared from the blood of 28 different donors. The blood groups of these individuals were as follows:

OMNRh+	10 donors
OMRh+	5 "
OMNRh-	3 "
OMRh-	2 "
ONRh+	1 "
ONRh-	1 "
A ₁ MNRh+	2 "*"
A ₁ MRh+	1 "
A ₂ MNRh+	1 "
BMRh+	1 "
A ₁ BNRh+	1 "

Total 28 donors

* Including patient.

The degree of agglutination in each tube was recorded, and it can be said that the

TABLE 2.—RESULTS OF TITRATION OF FIVE REPRESENTATIVE SERA WITH RED CELLS FROM 5 DIFFERENT GROUP O INDIVIDUALS

Serum	Cells	Dilution of serum					
		1:8	1:16	1:32	1:64	1:128	1:256
G. C.	W.V.	±	—	—	—		
	R.S.	+	±	—	—		
	A.R.	++	+ ±	+	±		
	J.T.	+	±	—	—		
	J.K.	+	±	—	—		
W. D.	W.V.	—	—				
	R.S.	—	—				
	A.R.	+	±				
	J.T.	±	—				
	J.K.	±	—				
J. K.	W.V.	+	—	—			
	R.S.	+	±	—			
	A.R.	+ ±	+	±			
	J.T.	+	±	—			
	J.K.	+	±	—			
M. W.	W.V.	..	+++	+++	++	+ ±	±
	R.S.	..	+++	+++	++	+	+
	A.R.	..	+++ ±	+++	++	+ ±	±
	J.T.	..	+++	+++	++	+	—
	J.K.	..	+++ ±	+++	++ ±	+	±
J. D.	W.V.	..	+++	++	+ ±	±	—
	R.S.	..	++	+ ±	+	±	—
	A.R.	..	++ ±	++	+	±	—
	J.T.	..	++	+	±	±	—
	J.K.	..	+++	++	+	±	—

The belief that potent sera may give the same results with all human cells was further supported by the following experiment:

Serial dilutions of the serum of patient M. S. were made in large volume, after which 0.5 ml. portions were distributed to small tubes. The serum was then titrated in the usual way with cell sus-

results with all cells were nearly identical (titer 1:1280 to 1:1920). On the following day fresh cell suspensions were prepared from the citrated, refrigerated whole blood of the 28 donors, and again the results were nearly identical.

An eluate was prepared from this same serum by absorbing the cold hemagglutinins with Group O cells (donor R. J.)

at refrigerator temperature. The serum was then removed, the agglutinated mass of cells washed with ice-cold saline and the antibodies finally eluted into warm saline which was added to a volume equal to that of the serum removed. The eluate thus prepared was likewise tested twice (2 days apart) with the cells of the 28 donors. Again the results with all cells were nearly identical (titer 1:640 to 1:960). The reactions were slightly but significantly weaker with the 2 day old cells.

Relative Sensitivity of Group O and Autologous Cells. In most of the investigations of cold hemagglutinins thus far reported, tests have been made with Group O cells. The wisdom of using the same Group O donor for all tests has been recognized by several authors, but unfortunately the same human donor is rarely available to any laboratory for a long period of time. In routine studies it will therefore be more convenient to test each patient's serum with his own cells, which will always be obtainable.

Investigations carried out in this laboratory indicate that absolute values obtained with autologous cells are not often significantly different from those obtained with highly sensitive Group O cells. Presumptive tests of 30 sera were set up in duplicate, using autologous and Group O cells (donor A. R.). Nine sera gave negative results with both types of cells, 10 gave identical reactions ranging from \pm to +++ with both types, 7 gave slightly stronger and 4 slightly weaker reactions with the Group O cells. The few titrations carried out in a similar manner showed that, in general, autologous cells are only slightly less sensitive than Group O cells from donors R. J., and A. R. slightly less sensitive than Group O cells from donors R. J. and A. R.

Optimal Concentration of Cells. The final concentration of red cells, after addition of cell suspension to diluted serum, ranges from 0.1 to 1% in the studies reported by other investigators. Use of the former concentration resulted in much

higher titers than the latter in the experience of the Fort Bragg Commission.⁴ Similar results were obtained in this laboratory but a final concentration of 0.5% was decided upon for routine use because of difficulty in gross detection of agglutination of the more dilute suspensions.

Freedman and Mirsky¹² reported tentatively that the longer cells were stored, the more readily were they agglutinated. On the contrary, the investigations of the Fort Bragg Commission⁴ and the less extensive studies carried out in this laboratory showed conclusively that red cells become much less sensitive to cold hemagglutinins after 3 or more days of storage. This was true even when sterile, citrated whole blood was stored in the refrigerator and the cells washed immediately before use; deterioration was more marked if the cells were stored in saline suspension. No loss of reactivity could be detected after 24 hours of storage, and the loss was minimal after 2 days of refrigeration.

All titrations recorded in the present clinical study were carried out with cells stored for less than 24 hours.

Period of Refrigeration of Serum-Cell Mixtures. There is general agreement that it is best to examine the serum-cell mixtures after refrigeration overnight for 14 to 18 hours. During the present study many tubes were inspected for agglutination after 1, 2, 4 and 18 hours of refrigeration at 4° C. Agglutination was nearly always maximal at 18 hours and the advisability of overnight refrigeration was evident.

Method of Examining Tubes. The technique used in inspecting tubes for the presence or absence of agglutination has already been described. In a number of instances the end-point of the titration was determined microscopically by transferring a drop of cell suspension to a plain glass slide and examining it under low power. Titers determined in this way were usually 1 tube higher than those read grossly, but it was felt that micro-

scopic observations offer no advantage because there is apt to be some irregularity in the extent to which the drop is warmed while being examined on the slide. Use of a hand lens is recommended by some, but gross inspection of cold hemagglutination is simpler and is apparently adequate.

Recording of Serum Dilutions. In this study all titers are recorded in terms of the final dilution of serum after addition of the cell suspension. The same policy was followed by the Fort Bragg Commission. Other authors, as noted in Table 5, either record titers in terms of original serum dilutions or fail to state their policy in this respect. Since the volume of cell suspension added is often much less than the volume of diluted serum, it is difficult to calculate the final serum dilution in these reports. In dealing with agglutination reactions of this type, much might be gained if all investigators chose to mix equal volumes of diluted serum and cell suspension and to report all titers in terms of the final dilution of serum.

Results of Tests for Cold Hemagglutinins. Survey of Hospitalized Patients and "Normal" Individuals. During the period beginning July 1, 1943, and ending Nov. 30, 1944, blood was collected from all adult patients admitted to the Strong Memorial and Rochester Municipal Hospitals and subsequently thought to be suffering from primary atypical pneumonia. The first specimen was drawn as soon as this disease was suspected in a given patient, and subsequent specimens at intervals of 2 to 10 days thereafter during the period of hospitalization. In some instances it was possible to obtain additional samples of blood after the patients had been discharged from the hospital. The final diagnosis of atypical pneumonia was based upon the clinical picture as a whole,^{7,31,46} apart from the results of the tests for cold hemagglutinins.

During the period beginning Nov. 15, 1943, and ending July 15, 1944, an additional effort was made to collect blood in a similar way from all adult patients

hospitalized with any type of infectious disease. It was impossible to carry out this program in full, but nevertheless, sera were collected from over 400 patients representing a wide variety of infectious illnesses. In addition, a number of specimens were drawn from patients with certain non-infectious disorders, particularly those associated with splenomegaly. Patients with acute illnesses were included in the series only if they had donated at least 1 specimen between 12 and 30 days (in most cases 12 to 20 days) after the onset of their symptoms. If blood had not been drawn during this interval, the case was placed in the unclassified group, which was, therefore, a heterogeneous "waste-basket" collection of cases but did not include any cases of atypical pneumonia. Results of tests of sera from patients with chronic diseases were tabulated without regard for the date of onset of illness. Of the 130 normal individuals whose blood was tested for the presence of cold hemagglutinins, 122 were medical students and the remainder were hospital personnel.

Altogether 1762 specimens of serum were collected from 987 persons and approximately 2000 separate tests were made for the presence of cold hemagglutinins (not counting presumptive tests of sera subsequently titrated). Many of the sera were titrated more than once, and in such cases the highest titer obtained was the one recorded for purposes of the survey.

Cold Hemagglutinins in Atypical Pneumonia. Table 3 shows the distribution of maximal titers reached by the various individuals according to type of illness. It is immediately apparent that high titers are uncommon except in primary atypical pneumonia, while low titers are encountered in a variety of diseases as well as in supposedly normal persons. However, it must be emphasized that lower titers may be of importance provided a rise or fall, or preferably both, can be demonstrated in serial tests of sera drawn during the patient's illness and convalescence. The changes in titer of cold hem-

agglutinins in the sera of 9 patients with maximal titers of 1:32 or 1:64 are shown graphically in Figure 1. All of these patients presented the familiar picture of atypical pneumonia.

Similar changes in titer were observed in most of the *acute* respiratory infections, other than atypical pneumonia, in which

maximal titers of 1:32 or more were reached. However, titers of 1:32 or above were produced in only 8.9% of these cases as compared with 80% in the group with atypical pneumonia (Table 4). Pneumococcal pneumonia, unclassified pneumonia, pulmonary tuberculosis, bronchitis, nasopharyngitis and influenza are

TABLE 3.—DISTRIBUTION OF MAXIMAL TITERS OF COLD HEMAGGLUTININS ACCORDING TO TYPE OF ILLNESS

Disease	Number of cases with maximal titer of												Total cases
	<4	4	8	16	32	64	128	256	512	1024	4096	16,384	
Primary atypical pneumonia	5	2	2	..	4	9	6	9	2	4	1	1	45
Pneumonia unclassified	36	13	2	3	3	2	..	1	60
Probable pneumococcal pneumonia	48	13	3	2	3	3	72
Pneumococcal pneumonia with bacteremia	9	4	1	2	2	..	1	19
Active pulmonary tuberculosis	24	4	1	1	3	2	35
Pulmonary infarction	8	2	10
Acute bronchitis	3	3	1	..	1	8
Chronic bronchitis	3	7	1	2	13
Bronchiectasis	1	3	1	5
Lung abscess	1	1	1	..	1	4
Acute nasopharyngitis	14	10	2	..	1	27
Influenza A (epidemic)	44	9	2	..	2	57
Acute catarrhal jaundice	3	2	1	1	7
Infectious mononucleosis	7	6	2	1	4	1	1	22
Rubella	1	1	..	1	3	3	2	11
Mumps without orchitis	1	1
Lymphocytic choriomeningitis	1	1
Herpes zoster	1	1
Poliomyelitis	..	8	1	9
Acute rheumatic fever	6	1	..	1	3	1	12
Endocarditis, <i>Strep. viridans</i>	2	1	..	1	4
Streptococcal (hemolytic) infections	8	5	1	1	1	1	17
Staphylococcal infections	..	1	1	..	1	3
Meningococcal infections	13	2	..	2	..	1	18
Gonococcal infections	3	3
Early syphilis	3	3
Bacillary dysentery (<i>Sonne</i>)	2	1	1	4
Malaria, <i>P. vivax</i>	1	1	2
Leukemia	8	3	11
Pernicious anemia	2	1	1	4
Sickle cell anemia	1	1	1	3
Congenital hemolytic jaundice	1	1	..	1	1	4
Acquired (atypical) hemolytic anemia	1	1	1	3
Congestive splenomegaly	..	1	1	2
Idiopathic thrombopenic purpura	1	1	2	1	5
Splenomegaly unclassified	..	2	..	2	..	1	5
Cirrhosis of liver	1	7	2	1	2	2	1	16
Unclassified diseases	236	58	17	14	2	4	331
"Normal" individuals	67	36	13	6	6	1	1	130
Total	564	211	59	39	44	33	16	13	2	4	1	1	987

TABLE 4.—INCIDENCE OF HIGH TITERS OF COLD HEMAGGLUTININS IN VARIOUS GROUPS

Group	Total No. cases	Total No. sera tested	Cases with maximal titer of			
			1:32 or higher		1:128 or higher	
			No.	%	No.	%
Atypical pneumonia	45	154	36	80.0	23	51.1
Other respiratory infections	291	700	26	8.9	2	0.7
All other diseases	521	768	44	8.4	11	2.1
"Normal" individuals	130	140	8*	6.2	1*	0.7
Total	987	1762	114	11.5	37	3.7

* The "normal" individual with a titer of 1:128 had been hospitalized 3 months previously because of an attack of "acute bronchitis." The "normal" person whose serum gave a titer of 1:64 had had atypical pneumonia 23 months previously.

the diagnoses of the 291 patients making up the group of miscellaneous respiratory infections. Although some of the patients with other types of acute infectious disease (rubella, infectious mononucleosis, catarrhal jaundice, etc.) developed cold

agglutinins in titers of 1:32 or more, these cases are not considered separately in Table 4 because they do not enter into the differential diagnosis of atypical pneumonia.

In the *chronic* diseases, particularly

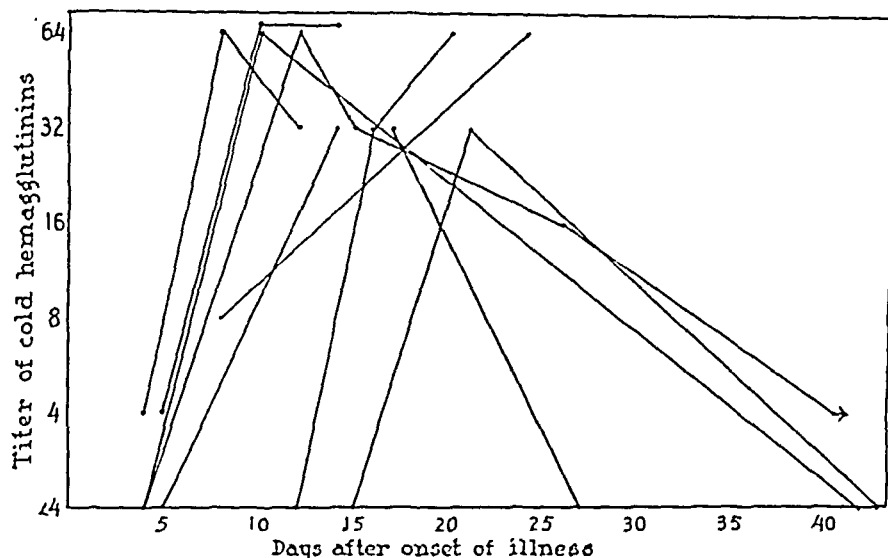


FIG. 1.—Rise and fall in titer of cold hemagglutinins in the sera of 9 patients with maximal titers of 1:32 or 1:64.

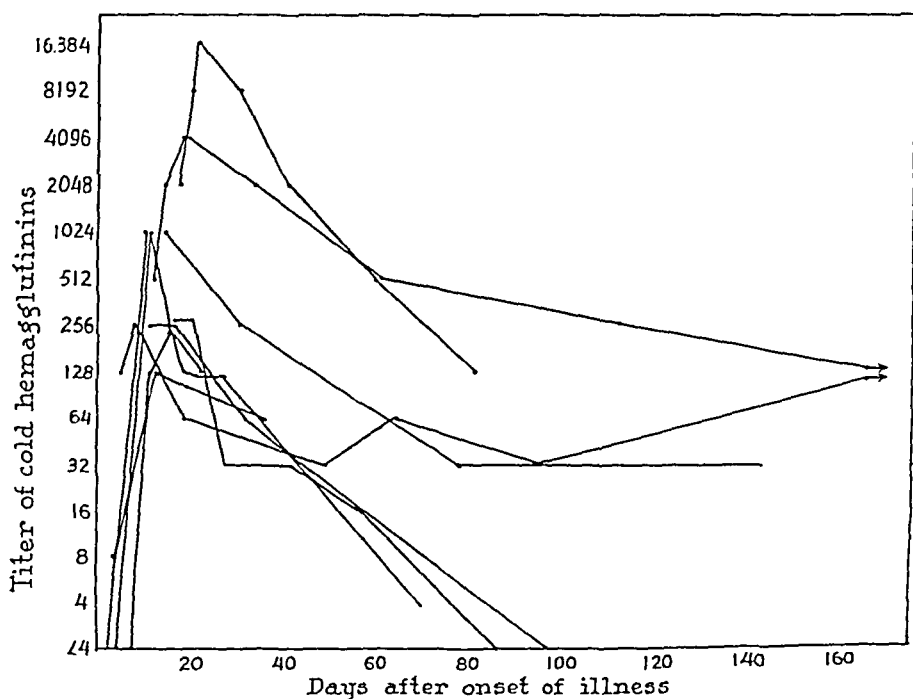


FIG. 2.—Rise and fall in titer of cold hemagglutinins in the sera of 10 patients with maximal titers of 1:128 or above. The specimen indicated by the upper arrow was drawn 7½ months after onset of illness; the lower arrow represents a specimen drawn at 10 months. The titer of both was 1:128.

those associated with splenomegaly, the titer of cold agglutinins remained relatively constant during the period of observation.

The rise and fall in titer of cold agglutinins in sera from 10 patients with maximal titers of 1:128 or above are plotted in Figure 2. It is apparent from Figures 1 and 2 that the titer of agglutinins usually rises most sharply during the 2nd week of illness and falls appreciably during the 4th week. This trend is also indicated in the hypothetical curve superimposed upon the dot graph of Figure 3.

ever, it is significant that she had not been hospitalized since the original bout of atypical pneumonia.

Titers of 1:128 or above were observed prior to the 5th day of illness in only 2 patients (Fig. 3). In both cases, illness began insidiously and the recorded dates of onset cannot be considered reliable.

McNeil³¹ found that titers were at their peak during the most serious stage of atypical pneumonia, which was 10 to 14 days after the onset of illness. At this time the fever was subsiding but pulmonary signs were most extensive and symp-

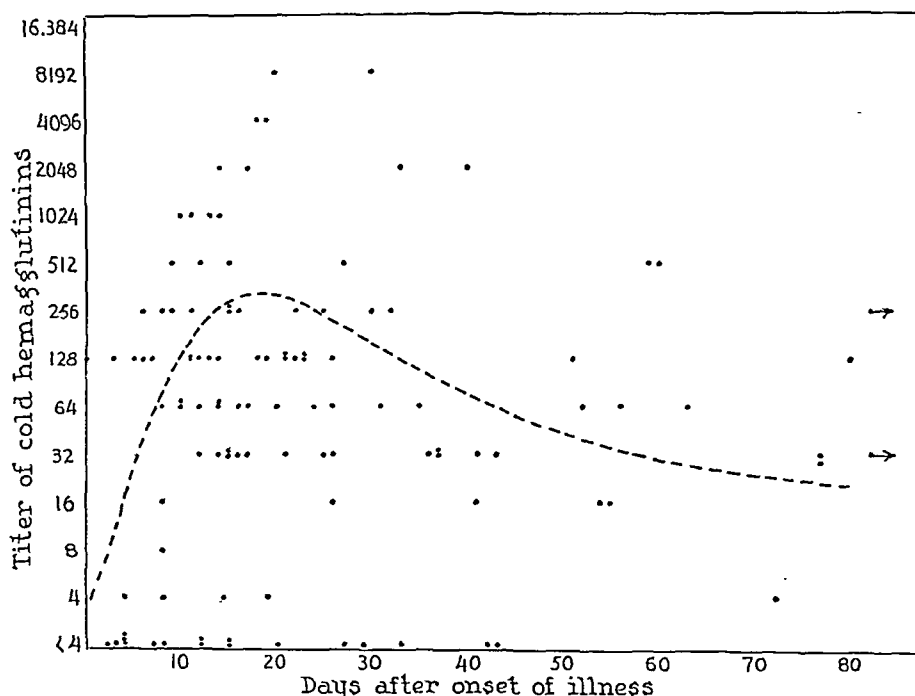


FIG. 3.—Titers of cold hemagglutinins in 115 sera drawn from 34 patients with primary atypical pneumonia at various intervals after onset of illness. The dotted hypothetical curve indicates the rise and fall in titer of a typical case during the period of illness and convalescence.

In several instances elevated titers persisted for periods of 4 to 10 months. The only patient who showed a significant rise in titer during this extended period of observation was a student nurse whose titer rose from 1:8 to 1:128 during the first 12 days of her illness. Three months later her titer had fallen to 1:32 but at 10 months had risen to 1:128. No information is available as to the occurrence of minor illnesses during this interval; how-

ever, it is significant that she had not been hospitalized since the original bout of atypical pneumonia. During the present study this sequence of events was observed only in the more severe cases. In the milder cases signs and symptoms were often maximal at 4 to 8 days, and the peak of the cold agglutinin titer was not reached until 15 to 20 days after the onset of illness.

Although some observers^{10,16,19,32} have found no correlation between the severity of the patient's illness and the height of

the titer of cold hemagglutinins, others^{4,9,35} have reported at least a rough relationship. The Fort Bragg Commission⁴ demonstrated a definite correlation between maximal titer and (1) number of days of fever above 100° F., and (2) extent of pulmonary involvement. In the present study, no such correlation could be shown. Some of the highest titers were recorded in relatively mild cases in which symptoms and signs were maximal 8 to 10 days before the peak of the agglutinin titer was reached.

Cold Hemagglutinins in Other Respiratory Infections. Unclassified pneumonias listed in Table 3 were those of uncertain etiology which did not follow the usual patterns of primary atypical pneumonia. Six out of 60 (10%) developed titers of 1:32 or above. One of these patients was a 71 year old woman who became ill rather suddenly and was found to have bronchopneumonia involving the left lower lobe. Three days after the onset of her illness, the white blood cell count was 22,500 per mm.,³ the cold agglutinin titer was 1:4, blood culture was negative and culture of the sputum revealed a predominance of *Streptococcus viridans*. The response to sulfadiazine was equivocal. The headache and persistent cough of atypical pneumonia were lacking. The titer of cold agglutinins rose to 1:256 on the 13th day of illness—a rise sufficient to suggest that this patient's illness may have been caused by the same agent responsible for many cases of more "typical" primary atypical pneumonia.

The 6 cases of probable pneumococcal pneumonia which developed titers of 1:32 or above were caused by organisms of Types 2, 3, 7, 14 and 16 and the 3 bacteremic cases by Types 5, 6 (titer 1:128) and 8. The bacteremic cases which failed to develop agglutinins in titers above 1:16 were caused by pneumococci of Types 1, 3, 5, 7, 8, 12, 18, 22 and 25.

Sera from 35 cases of active pulmonary tuberculosis were tested at various intervals after the onset of symptoms. When serial specimens were obtainable from the same individual, no appreciable variation

in titer could be demonstrated. However, most of these patients had probably been suffering from tuberculosis for 1 or more months before the first specimen was obtained. Three of the 35 patients had titers of 1:32 and 2 had titers of 1:64. In none of these 5 cases was there evidence suggesting concomitant infection with the agent of primary atypical pneumonia.

Siffert and Krautman,³⁹ Favour,⁹ and Fetterman *et al.*¹⁰ likewise found only low titers in a total of 106 tuberculous patients, and Bridge *et al.*² obtained completely negative results in a series of 45 cases. The latter authors, however, reported positive reactions (titer not stated) in 2 patients who were thought to have both atypical pneumonia and tuberculosis.

It can be concluded from these observations that the test for cold hemagglutinins is of some value in the differential diagnosis of tuberculosis and atypical pneumonia. Although a negative test has little significance, a positive result in high titer in a patient with pulmonary infiltration argues strongly for a diagnosis of atypical pneumonia. In such a case, however, the possibility of finding both diseases in the same patient cannot be entirely ignored.

The finding of a cold agglutinin titer of 1:256 in a patient with previously established *bronchiectasis* is of interest. This patient was acutely ill and febrile at the time of the test but there was no roentgenographic evidence of pneumonia. Unfortunately no conclusions can be drawn from this case because serial studies were impossible.

Grier¹⁵ found that in two-thirds of 40 cases of bronchiectasis a mistaken diagnosis of primary atypical pneumonia was made initially and later corrected when the patients were discovered to have pneumonitis around a preëxisting bronchiectasis. However, it is reasonable to suspect that some of the acute exacerbations seen in patients with this chronic disease may be due to infection with the specific agent or agents of primary atypical pneumonia. Moreover, it is possible that some cases of bronchiectasis are initiated by

attacks of atypical pneumonia in which it is known that patients suffer from bronchiolitis, peribronchiolitis and intractable cough.

The failure of epidemic *influenza* (December 1943 and January 1944) to cause the development of cold agglutinins in 57 closely followed patients serves to emphasize once more that this disease is distinctly different from atypical pneumonia.

Little can be said about the finding of a titer of 1:128 in the serum of a single patient who was convalescing from *catarrhal jaundice*.

Six of 22 patients with *infectious mononucleosis* developed titers of 1:32 or above. The diagnosis in each case was established by the appearance of abnormal lymphocytes in the peripheral blood and sheep cell agglutinins which were readily absorbed by bovine cells but not by guinea pig kidney.⁶ The development of cold agglutinins in infectious mononucleosis has been described previously by Belk,¹ McNeil,³¹ Freedman and Mirsky,¹² and Spingarn *et al.*,⁴⁰ but the significance of these agglutinins in this disease is not yet clear.

The appearance of cold agglutinins in titers of 1:32 or above during the 2nd or 3rd week of illness in 8 out of 11 cases of *rubella* is surprising, and indicates that further serologic investigations of this disease should be made. In the present study* *rubella* ranks second only to atypical pneumonia as a cause for the development of cold hemagglutinins. Favour⁹ reported a titer of 1:80 in a patient who had *rubella* 1 month after an attack of atypical pneumonia, but the titers found in 6 other cases were insignificant.

The occurrence of cold agglutinins in high titer in certain diseases associated with *splenomegaly* deserves special emphasis. A titer of 1:256 was repeatedly demonstrated over a period of 6 months in the serum of a patient with *sickle cell*

anemia and a markedly enlarged spleen. Sera from 2 other patients suffering from the same disease but having no *splenomegaly* did not contain significant amounts of cold agglutinins.

Four cases of *congenital hemolytic jaundice* were studied: 1. Serum from 1 patient was drawn and tested at 8 and again at 20 months after splenectomy; the titers of these intervals were 1:4 and 1:16 respectively.

2. The second patient had all of the usual manifestations of the disease except *splenomegaly*. A single specimen was tested and showed a titer of 1:32. Splenectomy was not performed.

3. In the third case the titer was 1:256 prior to splenectomy and 1:128 and 1:4 at 8 and 40 days after operation respectively.

4. The titers in the fourth case were 1:128, 48 days and 2 days before splenectomy and again 12 days after operation.

The occurrence of cold agglutinins in *acquired hemolytic anemia* is discussed in a separate paper.²⁷ In only 1 of 3 cases included in the present study was there a titer of any significance. In this case complete recovery followed splenectomy and the blood picture returned to normal, but the cold hemagglutinins persisted in undiminished titer for at least 6 months. In 1 of 5 cases of *idiopathic thrombopenic purpura* with *splenomegaly*, the titer was 1:128 on the day before splenectomy and 1:16, 3 weeks later.

The recorded instances of the association of cold agglutinins with *splenomegaly* are sufficient to arouse speculation, but much more work must be done before the significance of this relationship can be stated. The disappearance of agglutinins after splenectomy in some cases and the persistence of the same in others⁴² is puzzling. In this connection, it is of interest that Nakamura³³ found no change

* Ten of the 11 patients with *rubella* were Navy V-12 students from the College of Arts and Sciences of the University of Rochester. All became ill within a period of approximately 1 month. Lieutenant George Heckel, MC, USNR, very kindly assisted with the collection of serum from these patients and from many others in the same student body who were hospitalized because of various acute illnesses.

in the titer of cold hemagglutinins following splenectomy in normal rabbits.

The finding of cold agglutinins in some cases of *cirrhosis* of the liver is in accord with the experience of others.⁴²

Cold Hemagglutinins in Normal Individuals. Positive results were obtained with the sera from 63, or nearly one-half of a group of 130 normal persons most of whom were medical students. However, titers of 1:32 or above were recorded in only 8 instances. The student whose serum gave a titer of 1:64 had had atypical pneumonia 23 months previously, and the student with a titer of 1:128 had been hospitalized 3 months earlier because of an attack of acute bronchitis.

Among the 58 students in the class that had suffered heavily during an institutional outbreak of atypical pneumonia 15 months previously,⁴⁶ there was a slightly lower incidence of positive tests and lower average titer than among the 64 members of another class who had entered school a year after the outbreak occurred. In the former group were 17 students who had had clinically apparent atypical pneumonia, yet none of these students had a titer greater than 1:8 after the 15 month interval.

The so-called "normal" individuals comprising the above control group were normal only in the sense that they were in good health at the time their sera were tested. This group had to suffice because persons with strictly negative past histories, with regard to respiratory infection, are practically unobtainable in this latitude.

It should be emphasized that a negative result with the technique employed in this study does not indicate complete lack of agglutinins. Many more positive results would be recorded if the test tubes were examined microscopically. In 1 unselected group of 200 sera, 70 of the specimens gave negative presumptive tests but agglutination was detected in 32, or nearly one-half, of these 70 tubes when the serum-cell mixtures were checked under the low power of the microscope.

An even higher incidence of positive results could be obtained if the serum were separated from the clot at 37° C. and added to the cell suspension without any dilution.

Kettel's belief that cold hemagglutinins are present in *all* normal human sera (at least in minute amounts) is apparently well founded. He actually demonstrated these antibodies in 95% of 600 sera, most of which were collected from patients with chronic diseases.²² It is clear that the reported absence of agglutinins in the sera of many individuals can be attributed entirely to the use of crude technique.

Other Serologic Tests of Sera Containing Cold Hemagglutinins. Complement fixation tests with psittacosis antigen were kindly performed by Dr. K. F. Meyer who reported essentially negative results from 42 sera. These specimens had been drawn from 15 different patients who had atypical pneumonia and developed cold agglutinins in titers ranging from 1:32 to 1:4096. Suggestive results were obtained in only 3 cases and in none of these was there any history of contact with birds.

Peterson, Ham and Finland³⁵ have reported similar findings, while Meiklejohn³² and Levinson *et al.*²⁸ found little or no development of cold agglutinins in 4 patients shown to be infected with psittacosis-like viruses. These results serve to emphasize the fact that although psittacosis (or ornithosis) and primary atypical pneumonia of unknown etiology are clinically similar, they can be differentiated readily by serologic tests.

Sera containing cold agglutinins in high titer were tested with sheep cells at various temperatures. In addition most of the absorption studies reported by Clough and Richter,³ and Wheeler, Gallagher and Stuart⁴⁵ were repeated with similar findings. The results of these investigations are described elsewhere.⁴⁸

In addition an attempt was made to differentiate serologically the cold agglutinins found in patients with atypical pneumonia from those found in patients with hemolytic anemia, sickle cell ane-

mia, infectious mononucleosis and rubella. However, it was necessary to terminate this investigation before any positive results could be obtained.

Case Report. One of the most interesting cases encountered during the course of this study was that of a 23 year old white married woman who was thought at first to have lymphocytic choriomeningitis. She had begun to suffer severe headache 4 days before admission. Two days later she had fever and generalized aching and was given sulfadiazine without response.

On admission to the hospital Jan. 6, 1944, the temperature was 101.3° F., the neck was somewhat stiff, the throat was moderately injected and the lungs were clear. The white blood count was 9500 and the blood smear was normal. The spinal fluid contained 600 lymphocytes per c.mm. and 70 mg. protein per 100 ml. Cultures of the spinal fluid and blood were negative. A roentgenograph of the chest revealed increased density in the right cardiophrenic angle.

The patient improved rapidly and was discharged from the hospital 4 days after admission. On Jan. 10, 1944, the day that she returned to her home, sera collected on January 7 and 10 were tested and found to contain cold hemagglutinins in titers of 1:128 and 1:256 respectively. Additional specimens obtained on January 19 and February 12 yielded titers of 1:64 and 1:32 respectively. All of these sera were then tested for neutralizing antibodies against the virus of lymphocytic choriomeningitis with negative results.*

The patient's clinical history was checked thoroughly and it was found that she had had a dry cough for several days before admission and during her hospital stay, but said little about it to her attending physicians. After she returned to her home the cough became much more troublesome and productive. She was still coughing frequently when last questioned on Feb. 20, 1944.

It is unfortunate that attempts to isolate a virus from this patient were not made. Nevertheless, it seems likely, in retrospect, that the meningitis in this instance was caused by one of the agents currently responsible for many cases of atypical pneumonia.

McNeil³¹ mentions a case of lymphocytic choriomeningitis in which a cold agglutinin titer of 1:96 was found on the 8th day, but no details of this illness are given. Review of the literature reveals 9 cases of atypical pneumonia in which meningismus was a notable feature,^{13,18,25,29,36} in only 2 of these^{13,36} was the spinal fluid abnormal (lymphocytosis and elevated protein). The occurrence of encephalitis as a complication of atypical pneumonia is well established,^{8,14,21,31} but there is obviously need for further investigation of meningitides found in association with pneumonitis.

Complications Attributed to the Presence of Cold Hemagglutinins. Peripheral vascular occlusion,^{17,30,35,41} pulmonary infarction,^{31,35} and hemolytic phenomena^{5,19,35} have been observed by other investigators in patients whose serum contained cold agglutinins. As a rule, the agglutinins in these cases were found to have broad thermal amplitude and were often present in high titer.

With one exception, these complications were not observed during the present study in spite of the fact that 6 of the patients with atypical pneumonia developed titers of 1:1024 or above. Moreover, in 4 of these 6 cases, activity of the agglutinins at room temperature was readily demonstrable. The single exception was a patient with acquired hemolytic anemia whose course is described in detail elsewhere.^{27,47} Although the agglutinins in this case were present in a titer of only 1:128, they were active at 37° C. and were associated with phlebothromboses and the rapid destruction of both autologous and transfused cells.

Discussion. Technical. The technique of testing for the presence of cold agglutinins as herein described has proven satisfactory for investigative purposes. However, the following technique is suggested for routine hospital use.

Collect 5 to 10 ml. of blood in a sterile tube. Separate serum from the clot after standing at room temperature 1 to 3 hours. Insert 8 or more small test-tubes in a rack

* The neutralization tests were carried out by Dr. Charles Armstrong, Chief, Division of Infectious Diseases, National Institute of Health, Bethesda, Md.

and place 0.8 ml. physiologic saline solution in the first tube and 0.5 ml. in the remaining tubes. To the first tube add 0.2 ml. serum (which need not be inactivated); mix thoroughly with a 1 ml. pipette, make serial two-fold dilutions (1:5, 1:10, 1:20, etc.) and discard 0.5 ml. diluted serum from the next to the last tube. The last tube contains only saline and serves as a control.

Prepare an estimated 1% suspension of the patient's own red blood cells by washing cells from the clot with 5 to 10 ml. physiologic saline solution and washing the cells 3 times with an approximately equal volume of saline. To each tube of diluted serum add 0.5 ml. of the 1% suspension of cells which will thus double the dilutions of serum originally made. Shake rack to mix cells and serum and place in refrigerator at 4° C. overnight.

detectable agglutination. After the tubes have been examined, place them in an incubator or water-bath at 37° C. for 1 hour to determine whether or not the agglutination is reversible.

Whenever possible the test should be made on the day the blood is drawn. If it cannot be done until a later date, the serum which has been separated from the clot on the 1st day should meanwhile be stored at 4° C. (or kept in the frozen state) under sterile conditions. The patient's clot, from which cells are to be washed, can be used after 3 to 5 days, if necessary, provided a small amount of serum is left in the tube and it is stored in the refrigerator under sterile conditions.

Clinical. There is considerable difference of opinion among the various observers as to the value of the test for cold hemagglutinins in the differential diagno-

TABLE 5.—INCIDENCE OF "SIGNIFICANT" TITERS OF COLD HEMAGGLUTININS IN REPORTED CASES OF ATYPICAL PNEUMONIA

Authors	Titer regarded as significant	Serum dilution recorded	No. cases studied	Cases with significant titers	
				No.	%
Horstmann and Tatlock ¹⁹	1:4	Original	43*	27	63
Turner <i>et al.</i> ⁴⁴	1:32	Original	83	44	53
Shone and Passmore ³⁸	(Qualitative test only)		54	(54)	(100)
Meiklejohn ³²	1:40	Original	74	45	61
Fort Bragg Commission ⁴	1:64	Final	93	29	31
Streeter, Farmer and Hayes ⁴³	1:40	Original	50	20	40
Fetterman, Moran and Hess ¹⁰	1:32	Original	44†	29	64
Rich, Rae and McGoe ³⁷	1:64	Not stated	37	17	46
Freedman and Mirsky ¹²	1:32‡	Original	35	10	29
Favour ⁹	1:160	Original	46	18	39
Fowler ¹¹	1:20‡	Not stated	20	17	85
Humphrey ²⁸	1:4	Original	14	13	93
Present study	1:128	Final	45	23	51
Total			638	346	54

* The majority of the sera tested by Horstmann and Tatlock had been stored for 1 to 14 months.

† Heinzelman and Seligmann¹⁶ reported separately 33 of the 44 cases reported by Fetterman *et al.*

‡ Titer selected by present author.

Examine tubes immediately after their removal from the refrigerator by holding them in a nearly horizontal position over a well-illuminated white background. Shake each tube gently but quickly until all cells in the bottom have been dislodged. Record the titer in terms of the final dilution (1:10, 1:20, 1:40, etc.) of the serum in the last tube showing grossly

sis of primary atypical pneumonia. Rich *et al.*³⁷ conclude that "the test, at present, has no value," and Freedman and Mirsky¹² obtained positive results in high titer as frequently with sera from patients with infectious mononucleosis as from patients with atypical pneumonia. On the other hand, Peterson, Ham and Finland,³⁵ Horstmann and Tatlock,¹⁹ Shone and Pass-

more,³⁸ and Humphrey²⁰ found cold agglutinins in nearly all cases of atypical pneumonia examined. Moreover Humphrey suggests that the test for cold agglutinins might even supplant roentgenographs of the chest in suspected cases of this disease.

The combined observations reported to date (Table 5) indicate that cold agglutinins appear in about one-half of all cases. This is only a very rough figure, however, because the denominator, that is, the total number of cases observed, cannot be reckoned accurately due to lack of clinical criteria for differentiation of atypical pneumonia from other respiratory infections. Moreover, it is likely that the syndrome known today as primary atypical pneumonia is produced by multiple agents, and perhaps only one of these is capable of stimulating the development of cold agglutinins. This suggestion is supported by the observations of McNeil³¹ who found that these heterophil antibodies appeared in all of 15 patients with this disease during a fall epidemic, but in none of the cases observed by him during a winter period. During the present study no seasonal correlations could be made, and patients with and those without cold agglutinins presented essentially the same clinical features.

The test for cold hemagglutinins, like other agglutination reactions, is seldom helpful during the 1st week of illness, when accurate diagnosis is most difficult and most needed. By the 2nd week, when agglutinins appear, the diagnosis is often already established on the basis of clinical course and lack of response to sulfonamide therapy. Nevertheless, the confirmatory value of a positive test for cold agglutinins is apparent, especially in prolonged and "atypical" cases.

Final evaluation of this test cannot be made until more is known about the etiology of atypical pneumonia and about the mechanism by which these peculiar antibodies develop. In the meantime, however, it is urgent that whenever possible tests for cold hemagglutinins be

carried out in all cases of pulmonary infection of uncertain etiology. It is particularly important that this be done in certain cases, such as those cited individually in this report.

Further studies of this type may aid materially in piecing together the varied clinical manifestations produced by one or more of the agents responsible for what is now called primary atypical pneumonia. Moreover, extensive use of this test during epidemics may be of great value in investigating the epidemiology of this increasingly important disease.

Summary. 1. Various factors affecting the results of tests for cold hemagglutinins were investigated and a test for routine use was proposed.

2. During a period of 17 months, 1762 specimens of serum were collected from 987 persons and examined for their content of cold hemagglutinins. Included in this study were 154 sera from 45 patients with primary atypical pneumonia; results with this group were as follows:

(a) Only 51% of these patients developed titers of 1:128 or higher which were above the range frequently encountered in other diseases and in normal individuals. Titers of 1:32 or above appeared in 80% of these cases and the *development* and *disappearance* of agglutinins in these lower titers was thought to be of added significance.

(b) Titers rose rapidly during the 2nd week of illness and fell during the 4th week but in some instances they remained elevated for 2 to 10 months. In severe cases the peak of the titer coincided with the period of maximal signs and symptoms (10 to 14 days) but in milder cases signs and symptoms were most pronounced at 4 to 8 days while the peak of the agglutinin titer was not reached until 15 to 20 days after the onset of illness.

(c) No relationship between titer and severity of illness could be demonstrated.

(d) The development of cold hemagglutinins during the 2nd week in a patient with pulmonary infection of unknown etiology appeared to be of distinct value in confirming the clinical impression of

primary atypical pneumonia. The value of the test for cold agglutinins in the diagnosis of certain "atypical" cases could not be estimated accurately because of lack of information concerning the etiology of these cases.

3. In 291 patients with respiratory infections other than atypical pneumonia and in 521 patients with a wide variety of other diseases, cold agglutinins were usually found only in low titer, except in rubella, infectious mononucleosis and in certain disorders associated with splenomegaly. Splenectomy had a variable effect upon the titer of agglutinins. Only 2 out of 130 "normal" individuals were found to have borderline titers, and in both instances a history of recent pulmonary infection was obtained.

4. A limited attempt to differentiate serologically the cold agglutinins found in patients with various disorders was unsuccessful.

5. Phlebothromboses and hemolytic phenomena were observed in association

with the presence of cold agglutinins in a single case—a patient with acquired hemolytic anemia. None of the patients with atypical pneumonia developed complications that could be attributed to the presence of cold hemagglutinins, even though these antibodies were sometimes present in very high titer and were active at room temperature.

Conclusion. 1. A simple quantitative test for cold hemagglutinins is recommended for addition to the armamentarium of clinical laboratories.

2. Liberal use of this test can be expected to aid:

- (a) In diagnosis of atypical pneumonia.
- (b) In further defining the conditions under which cold hemagglutinins are produced.
- (c) In explaining certain vascular and hemolytic disorders.
- (d) In clarifying the nature of these peculiar antibodies.

The encouragement and advice of Dr. John S. Lawrence throughout the course of this study is gratefully acknowledged.

REFERENCES

1. BELK, W. P.: *J. Lab. and Clin. Med.*, **20**, 1035, 1935.
2. BRIDGE, E., THURSTON, A., and REPICCI, A.: *J. Lab. and Clin. Med.*, **29**, 936, 1944.
3. CLOUGH, M. C., and RICHTER, I. M.: *Bull. Johns Hopkins Hosp.*, **29**, 86, 1918.
4. Commission on Acute Respiratory Diseases, Fort Bragg, N. C.: *Am. J. Med. Sci.*, **208**, 742, 1944.
5. DAMESHEK, W.: *J. Am. Med. Assn.*, **123**, 77, 1943.
6. DAVIDSOHN, I.: *J. Am. Med. Assn.*, **108**, 289, 1937.
7. DINGLE, J. H., and FINLAND, M.: *New England J. Med.*, **227**, 378, 1942.
8. Editorial: *Med. J. Australia*, **2**, 41, 1944.
9. FAVOUR, C. B.: *J. Clin. Invest.*, **23**, 891, 1944.
10. FETTERMAN, G. H., MORAN, T. J., and HESS, W. R.: *U. S. Nav. Med. Bull.*, **43**, 1128, 1944.
11. FOWLER, R. H.: Personal communication to Levinson *et al.*²³
12. FREEDMAN, A. M., and MIRSKY, I. A.: *Mil. Surg.*, **95**, 512, 1944.
13. GLENDY, R. E., BEASER, S. B., and HANKINS, W. D.: *Arch. Int. Med.*, **75**, 30, 1945.
14. GOLDEN, A.: *Arch. Path.*, **38**, 187, 1944.
15. GRIER, G. S., 3rd: *Arch. Int. Med.*, **73**, 444, 1944.
16. HEINTZELMAN, J. H. L., and SELIGMANN, A. W., JR.: *U. S. Nav. Med. Bull.*, **43**, 433, 1944.
17. HELWIG, F. C., and FREIS, E. D.: *J. Am. Med. Assn.*, **123**, 626, 1943.
18. HORNIBROOK, J. W., and NELSON, K. R.: *U. S. Pub. Health Rep.*, **55**, 1936, 1940.
19. HORSTMANN, D. M., and TATLOCK, H.: *J. Am. Med. Assn.*, **122**, 369, 1943.
20. HUMPHREY, A. A.: *U. S. Nav. Med. Bull.*, **43**, 1117, 1944.
21. INGLEBY, H.: *Arch. Path.*, **37**, 359, 1944.
22. KETTEL, K.: *Acta path. et microbiol., Scandinav.*, **5**, 306, 1928.
23. KETTEL, K.: *Compt. rend. Soc. de biol.*, **100**, 371, 1929.
24. KETTEL, K.: *Undersøgelser over Kuldehaemagglutinin* 1. *Mednes Kserum*, Levin and Munksgaard, 1930.

25. KNEELAND, Y., JR., and SMETANA, H. F.: Bull. Johns Hopkins Hosp., **67**, 229, 1940.
26. LANDSTEINER, K., and WITT, D. H.: J. Immunol., **11**, 221, 1926.
27. LAWRENCE, J. S., and YOUNG, L. E.: In preparation.
28. LEVINSON, D. C., GIBBS, J., and BEARDWOOD, J. T., JR.: J. Am. Med. Assn., **126**, 1079, 1944.
29. MARKHAM, J.: Canad. Med. Assn. J., **47**, 133, 1942.
30. McCOMBS, R. P., and McELROY, J. S.: Arch. Int. Med., **59**, 107, 1937.
31. McNEIL, C.: AM. J. MED. SCI., **209**, 48, 1945.
32. MEIKLEJOHN, G.: Proc. Soc. Exp. Biol. and Med., **54**, 181, 1943.
33. NAKAMURA, I.: Keijo. J. Med., **2**, 425, 1931.
34. OWEN, C. A.: Arch. Int. Med., **73**, 217, 1944.
35. PETERSON, O. L., HAM, T. H., and FINLAND, M.: Science, **97**, 167, 1943.
36. REIMANN, H. A.: J. Am. Med. Assn., **111**, 2377, 1938.
37. RICH, C. B., RAE, M. V., and MCGOEY, C. J.: Canad. Med. Assn. J., **51**, 239, 1944.
38. SHONE, S., and PASSMORE, R.: Lancet, **2**, 445, 1943.
39. SIFFERT, R. S., and KRAUTMAN, B.: J. Lab. and Clin. Med., **29**, 270, 1944.
40. SPINGARN, C. L., JONES, J. P., and OWRUTZKY, B.: U. S. Nav. Med. Bull., **43**, 717, 1944.
41. STATS, D., and BULLOWA, J. G. M.: Arch. Int. Med., **72**, 506, 1943.
42. STATS, D., and WASSERMAN, L. R.: Medicine, **22**, 363, 1943.
43. STREETER, G. A., FARMER, T. W., and HAYES, G. S.: Bull. Johns Hopkins Hosp., **75**, 60, 1944.
44. TURNER, J. C., NISNEWITZ, S., JACKSON, E. B., and BERNEY, R.: Lancet, **2**, 445, 1943.
45. WHEELER, K. M., GALLAGHER, H. J., and STUART, C. A.: J. Lab. and Clin. Med., **24**, 1135, 1939.
46. YOUNG, L. E., STOREY, M., and REDMOND, A. J.: AM. J. MED. SCI., **206**, 756, 1943.
47. YOUNG, L. E.: J. Immunol. (in press).
48. YOUNG, L. E.: (In preparation.)

CLINICAL ARREST IN ENTEROCOCCAL ENDOCARDITIS*

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ENDOCARDITIS due to infection of the cardiac valves with *Streptococcus fecalis*, the enterococcus of Thiercelin, is well recognized by students who have given careful attention to the bacteriology of endocarditis, but this particular infection has been too much neglected in the clinical reports. Thus Lloyd-Jones,² in the Appendix to the monograph of Perry³ on bacterial endocarditis, mentioned "*Str. faecalis* or the enterococcus which occasionally produces endocarditis in man," while the principal author, in a table facing page 20, lists the microbic findings in 1000 well-authenticated cases of bacterial endocarditis in the literature from Harbitz (1899) to 1933 without any mention of the enterococcus. In general, this organism appears to have been called *S. viridans* without any attempt to differentiate within the viridans group. From our own experience we should estimate that about 10 to 15% of patients with bacterial endocarditis are infected with the enterococcus (*S. faecalis*) as compared with about 60% infected with *S. salivarius*. The 2 species may be differentiated by behavior in cultures and by morphologic differences but of greater practical significance is the usual susceptibility of the salivarius strains to the bacteriostatic action of penicillin and their resistance to bacteriophages in contrast to the greater resistance of the fecalis strains to penicillin and their usual susceptibility to lysis by enterococcus bacteriophages. Bacterial endocarditis is all too often a wholly cryptogenic infection but sometimes it is possible to recognize antecedent disease

of the intestine, of the uterus or more especially of the urinary tract in enterococcus endocarditis, while extraction of a tooth or other trauma to the mucous lining of the mouth, nose or pharynx is a more frequent antecedent in the infection of the heart valves by *S. salivarius*.

Recovery or arrest of the disease in patients with enterococcemia must be very rare. Ribeyro⁴ has observed one such recovery in a patient who suffered from low-grade fever from Aug. 13, 1922, to Feb. 10, 1923, from whose blood the enterococcus was obtained by culture taken on January 17. This was not considered a case of endocarditis although the author was quite familiar with the association of enterococcus with bacterial endocarditis. Baehr¹ has shown 1 patient who apparently recovered from enterococcus endocarditis after treatment with large amounts of penicillin to maintain a blood level of 1.2 to 1.6 units of penicillin per ml. Apparently the last positive blood culture was observed some time in May 1944 in this patient.

We wish to present the summarized clinical chart together with brief discussion of 1 patient who has been observed for a considerable period and now appears to be in a state of arrest of this disease.

Case Report. P. M., male, aged 34, was born in New York City on Sept. 6, 1909, of Russian-Jewish parents. Evidently he was vigorous as a youth and played on the football team during high school years. In 1927 a heart murmur was discovered during a routine physical examination and he was sent to the cardiac clinic of the out-patient

* Aided in part by a Grant of the United Hospital Fund of New York City and by Grants No. 500 and No. 501 of the Com. on Therapeutic Research, Council on Pharmacy and Chemistry, Am. Med. Assn.

department of the New York Post-Graduate Hospital, where his first record is under date of Oct. 21, 1927. He then weighed 175 $\frac{3}{4}$ lbs. (70.7 kg.) and was 67 in. in height. He came to this clinic at intervals until Dec. 1, 1932. The record indicates chronic cardiovascular disease with aortic insufficiency of unknown etiology. He was not seen here again for nearly 11 years. On Feb. 15, 1943, he was again located and he reported to the clinic in response to a follow-up request. He had remained well during the entire intervening period, was now married and established in

About Dec. 23, 1943, he suffered an attack of sharp pain in the right lower abdomen, accompanied by nausea and vomiting. On the next day the pain had shifted to the right upper lumbar region. After roentgenologic examination, his physician told him that he had no kidney stone and no appendicitis but there was a small amount of blood in the urine, discovered on microscopic examination. On or about Jan. 2, 1944, he first experienced pains localized in small areas, especially in the hands and feet. Some of these painful areas were marked by

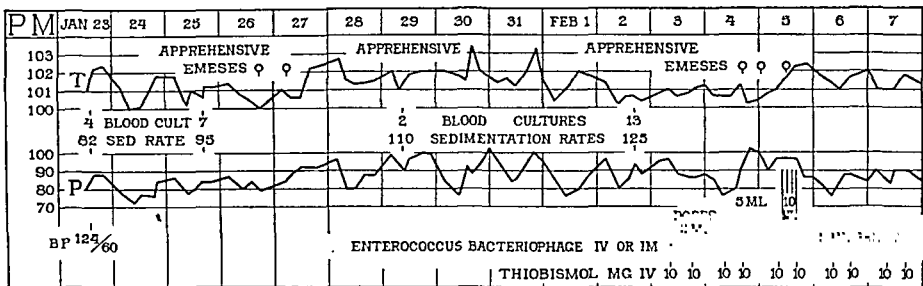


CHART 1

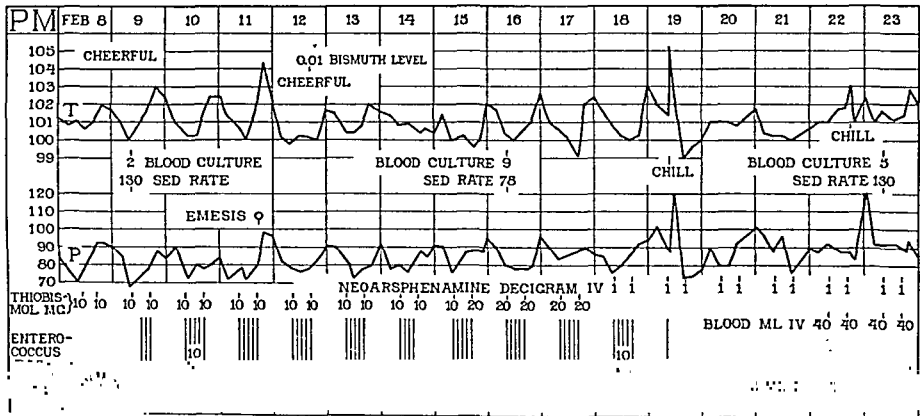


CHART 2

business and had been able to engage in strenuous activities. On March 8 he again appeared at the clinic, at which time there was an enlarged left ventricle, aortic insufficiency, regular sinus rhythm and electrocardiographic evidence of intraventricular conduction disturbance, myocardial damage and a suggestion of congenital heart disease, although a rheumatic etiology was regarded as worthy of consideration. The erythrocyte count was 6,230,000 and the sedimentation rate 11 mm. in 1 hr. He was dismissed with advice to return in 1 yr.

visible red spots under the skin, tender to pressure. His physician advised him to take his temperature every evening and he found an evening rectal temperature of 102° and normal temperature in the mornings. He was hospitalized near his home from Jan. 13 to 23. From Jan. 2 to 23 he lost 22½ lbs. (10.2 kg.) although his appetite has remained good.

On Jan. 23, 1944, he was transferred to the Post-Graduate Hospital. Physical examination on admission revealed enlargement of heart to the left; systolic blood

completely inhibited growth in the test tube and 0.1 mg. gave slight inhibition, while 0.01 mg. per 100 ml. of medium exerted no perceptible inhibitory effect upon growth. Penicillin, 25 units per ml. of medium, did not kill the streptococcus but permitted successful transplantation after exposure for 18 hrs. at 37°. A concentration of 5 units per ml. inhibited growth in the test tube

viously been granted to use penicillin to treat this patient, was immediately rescinded. The streptococcus was found to be susceptible to lysis by enterococcus bacteriophages and a specific bacteriophage active against this organism was prepared and available for use on Feb. 3. During this period of preliminary study from Jan. 23 to Feb. 3, the patient, his relatives and friends were

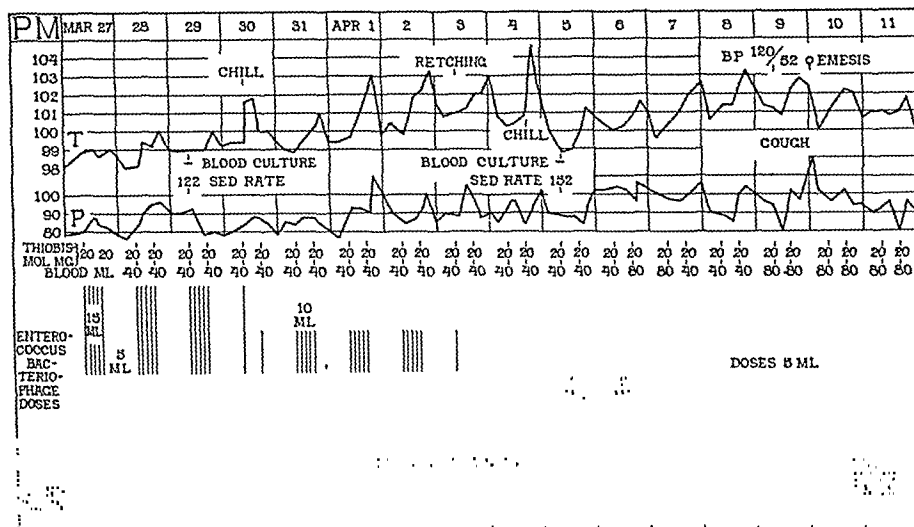


CHART 5

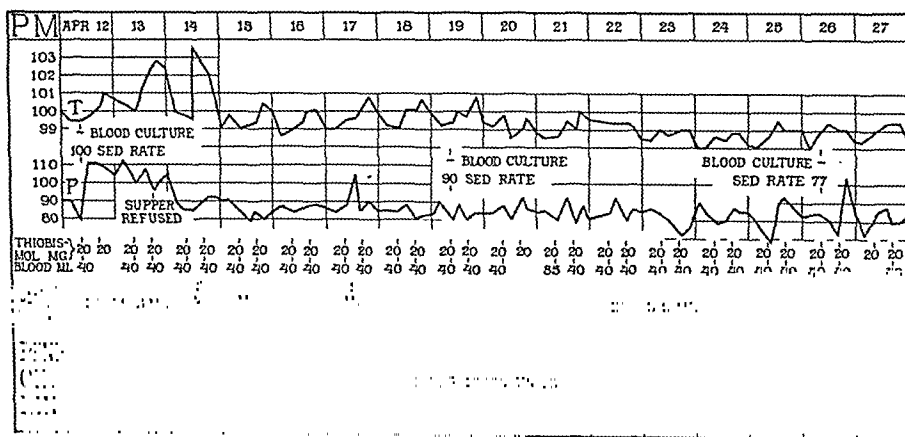


CHART 6

and a concentration of 0.625 unit per ml. exhibited slight inhibition as compared with the control broth. The same penicillin exhibited complete bacteriostatic effect upon a standard culture of staphylococcus (F.D.A. 209) in a dilution of 0.02 unit per ml. of medium. When these results were reported to the Committee in control of penicillin distribution, the permission, which had pre-

very apprehensive and impatient with the inaction and delay and especially perturbed because penicillin was not being administered.

The hospital record is summarized in the charts, each covering a period of 16 days. The temperature reached 103.4° on Jan. 30 and 103.2° on Jan. 31, and the sedimentation rate was 125 mm. in an hour on Feb. 2.

larger doses were again administered from March 19 to April 2. The thiobismol was increased to 20 mg. twice a day on March 15 and continued at this level. On March 23 the left thumb was swollen and tender, apparently because of a rather deep embolic lesion; the patient was emotionally disturbed and vomited and he was very unhappy because he was not receiving penicillin. A

experimental therapy. This calcium preparation was given in doses of 5000 units beginning at 12:15 noon on March 25, by intravenous injection during the day and by intramuscular injection at night. As a rule, the penicillin contained in 1 ml. of sterile distilled water was mixed with the bacteriophage just before injection and this mixture ordinarily developed a slight cloudy floccula-

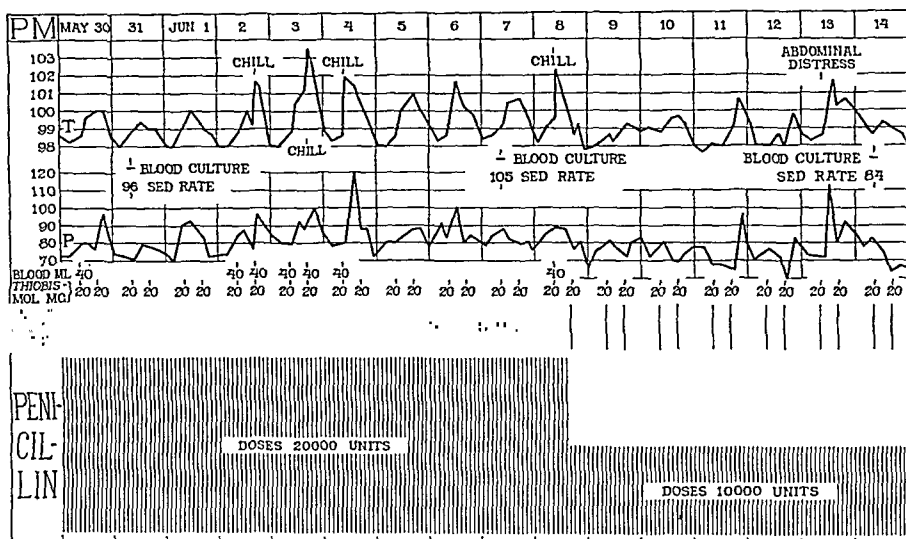


CHART 9

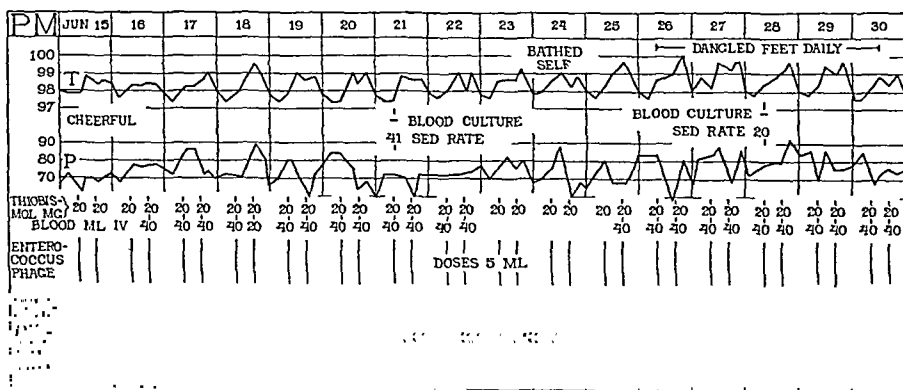


CHART 10

partially processed extract of the mold culture, in phosphate buffer solution, was administered by intramuscular injection in doses of approximately 1200 units ever 2 hrs., beginning at 2:15 p.m. March 23; this was stepped up to doses of 2000 units on March 24. We were then fortunate enough to obtain a supply of purified dry penicillin calcium which was apparently not acceptable for general use and therefore available for

tion. The remarkable improvement in the temperature curve from March 23 to 29 would seem to have resulted from the addition of penicillin to the therapeutic program but the improvement was so prompt that a psychic influence might be considered. However, the first negative result of blood culture was observed in the specimen taken on March 29.

A test of the susceptibility of the invading

organism to penicillin had been made only from the early cultures recovered before bacteriophage therapy was instituted and no great change in the susceptibility was anticipated. However, studies of the streptococcus from the blood culture of March 22 revealed it to be morphologically and culturally similar to streptococci of the salivarius rather than the enterococcus group, resistant to bacteriophagic action *in vitro* and so susceptible to penicillin that an estimated 0.0049 Oxford unit completely prevented

On March 26 there was a tender spot over the left 9th rib in the nipple line but no visible lesion. The spleen was not palpable. On March 29 there was a distinct embolic hemorrhagic spot in the ball of the right great toe, which was painful. A new lot of specific bacteriophage was brought into use on March 31 and this seemed to be more potent than the preceding preparation. The phage doses were maintained at 5 ml. or less for a long time after April 3. In spite of the continued small transfusions the patient re-

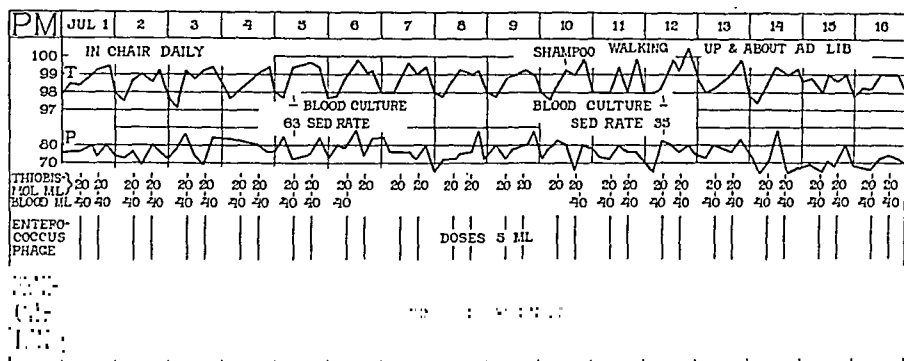


CHART 11

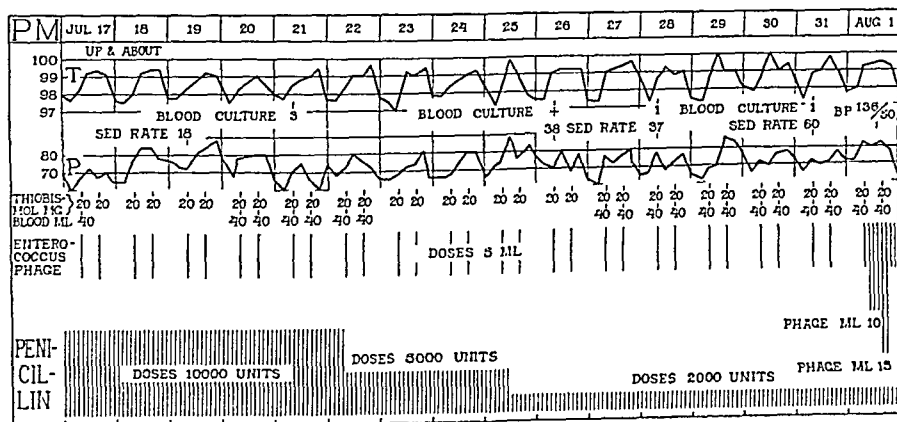


CHART 12

growth. The results of these studies, which were not available until April 9, may explain in part the very remarkable and totally unexpected response to penicillin therapy. The possibility of a second invader was considered, and though unlikely, cannot be disproved in this instance. The more acceptable theory is that the disease had been kept active by bacteriophage-resistant, penicillin-susceptible mutation forms of the original enterococcus after the bacteriophage-susceptible fraction had been overcome.

mained moderately anemic and his sedimentation rate continued to be unsatisfactory. On April 10 the dose of penicillin calcium was increased to 10,000 units every 2 hrs. and maintained at this level until May 26. During this time the general condition seemed to be improving, the blood cultures remained negative and the temperature tended to remain below 100° F. Nevertheless the sedimentation rate continued to be unsatisfactory. The dose of penicillin calcium was increased to 20,000 units every 2 hrs.

on May 26 and continued at this level until June 8.

During the first part of June there were several disturbances of temperature and some actual chills without other untoward manifestations. The small transfusions were omitted for a time but still there remained some elevation of temperature. On June 8

The clinical record from July 1 to 31 was regarded as satisfactory and the 2 daily doses of phage were continued while the penicillin was reduced to 5000 units every 2 hours on July 22 and further reduced to 2000 units every 2 hours on July 25. The blood culture taken on July 21 developed positive growth representing 3 organisms

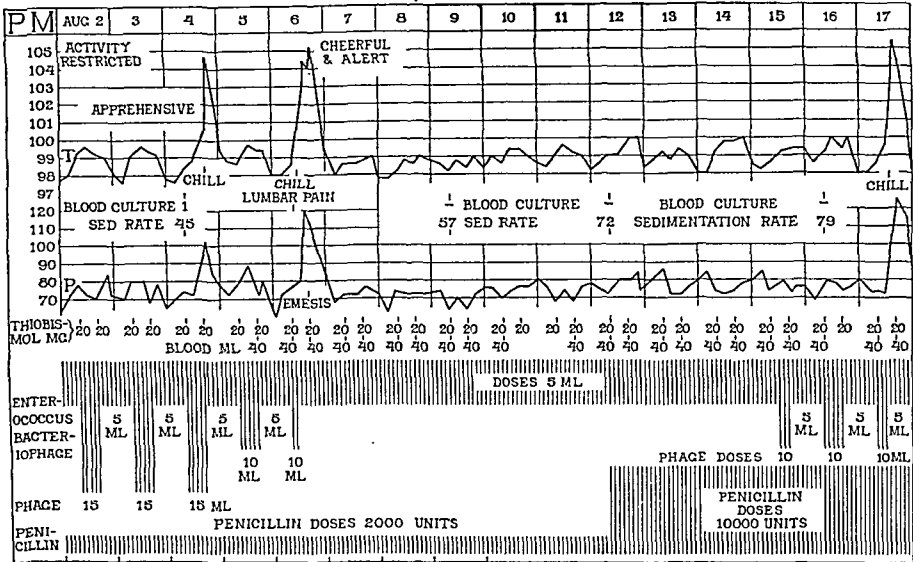


CHART 13

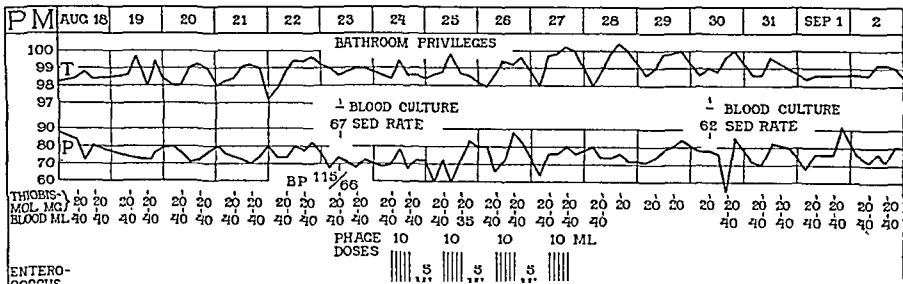


CHART 14

the bacteriophage doses were decreased to 5 ml. only twice a day and the penicillin was reduced to 10,000 units every 2 hrs. The record after June 14 suggests that the previous treatment may have been too drastic. Even the sedimentation rate came down on June 28. Greater activity was permitted and the patient seemed to be convalescent.

per ml. of the patient's blood, but this finding was not accepted as valid in the face of the other evidence of clinical improvement. However the bacteria, assumed to represent accidental contaminants, were subjected to searching study in the laboratory and by August 1 it became certain that they were of the same types as the streptococci of the many earlier blood cultures of this patient

August 2, 3 and 4 was 110 ml., representing an 11-fold increase. These doses were somewhat diminished after the reaction on August 4 and again on August 6. The blood specimens taken on August 9 and 12 gave negative cultures, although the doses of penicillin had been kept at the former level of 2000 units every 2 hrs. It might,



On August 1 the doses of bacteriophage were again scheduled at intervals of 2 hrs. day and night and some larger individual doses were given. Whereas the total daily amount had previously been 10 ml. from June 8 to July 31, the total daily amount on

perhaps, have been an interesting experiment to have discontinued the penicillin altogether at this time, but we felt that this agent was having some bacteriostatic effect and its omission could not be justified. The dose was therefore increased to 10,000 units every 2 hours on August 12. The activity of the patient had been restricted

again on August 2 but he was again granted bathroom privileges on August 23.

The record from September 3 to 20 was fairly satisfactory. The patient was eating well and gaining in weight and strength. There were untoward incidents, however, such as that on September 4. On September 20 the patient complained of precordial

creased to 20,000 units every 2 hrs. and the bacteriophage doses were also stepped up. The reaction on September 24 persuaded us to reduce the phage dose again and on September 30 one dose, that due at 4 15 P.M., was omitted. At the beginning of October the patient became more cheerful and optimistic.

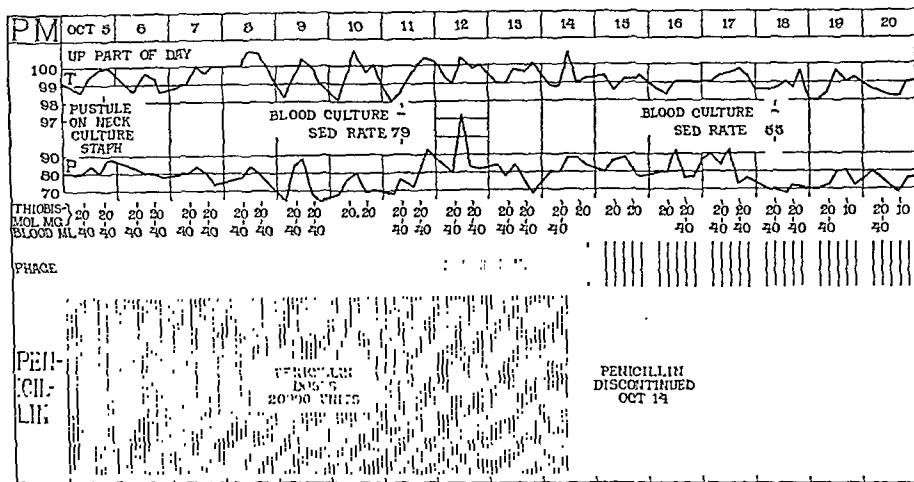


CHART 17

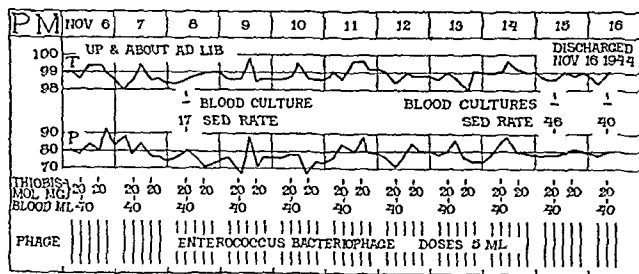
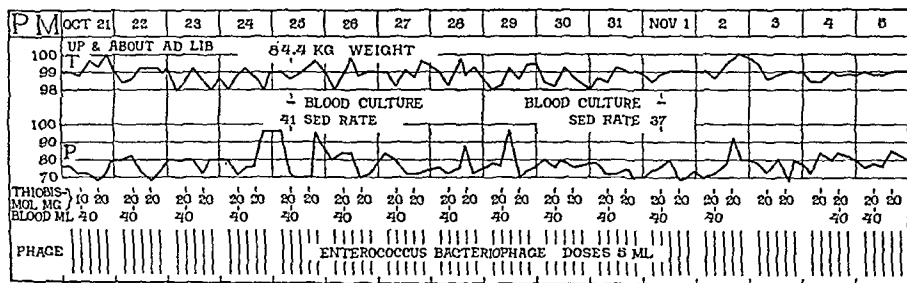


CHART 18

discomfort and irritation of his eyes but he was willing to admit that it might be that he was just uneasy and apprehensive and wanted to be reassured about his progress. However, his sedimentation rate was 105 mm. in 1 hr. on this day. Therefore, on September 21 the penicillin was again in-

A small furuncle which appeared on the neck, October 5, yielded a culture of staphylococcus. This lesion was needled with staphylococcus bacteriophage and healed promptly. Its origin during the period of high penicillin dosage was a matter of interest. The patient was now very well nour-

ished, weighing 180 lbs. (81.6 kg.) and his general condition was so satisfactory that the penicillin was discontinued on October 14 and the doses of enterococcus phage cut to 4 in the period of 24 hrs., thus permitting a period of uninterrupted rest at night. The sedimentation rate still remained unsatisfactory. There seemed to be inadequate reason to prolong further his period of hospitalization and he was discharged on November 16. Since that time he has reported in person 3 times a week and on each occasion has received an intravenous injection of 5 ml. of his specific enterococcus bacteriophage. On November 29 he weighed 201 lbs. (91.2 kg.). A reducing diet has now been prescribed. On March 7, 1945, his condition was excellent.

Dec. 6, 1945. This patient has remained free from recurrent activity of his bacterial endocarditis and is actively engaged in business and in good condition when shown before a gathering of physicians on this date. Cultures of the blood, taken on 23 occasions since December 1944, have given negative result. The sedimentation rate has varied from 5 mm. in an hour on Aug. 30, 1945 to 78 mm. in an hour on Oct. 3, 1945, following an acute respiratory infection. A persistence of rheumatic disease is suspected and the patient is still reporting for examination at frequent intervals. On Dec. 6, 1945 the sedimentation rate was 30 mm. in 1 hour.

The partially processed penicillin was generously supplied by Rare Chemicals, Inc., Flemington, N. J., and the calcium salt of penicillin to a total of approximately 26 million units by Chas. Pfizer, Inc., Brooklyn, N. Y., for which we wish to make grateful acknowledgment.

REFERENCES

1. BAEHR, G.: Penicillin Treatment of Subacute Bacterial Endocarditis Due to Enterococcus, Regional Meeting, Am. Coll. Phys., State of New York, New York City, October 1944.
2. LLOYD-JONES, D. M.: Appendix to Bacterial Endocarditis: An Experimental Study of Malignant Endocarditis by C. Bruce Perry, Bristol, John Wright & Sons, p. 128, 1936.
3. MAC NEAL, W. J., and BLEVINS, A.: Bacteriological Studies in Endocarditis, presented at the Meeting of the New York City Branch of the Society of American Bacteriologists, December 1944; abstract to appear in Proceedings.
4. PERRY, C. BRUCE: Bacterial endocarditis. Bristol, John Wright & Sons, p. 128, 1936.
5. RIBEYRO, R. E.: Enterococcemia, *Cronica medica*, 44, 4, 1927.

This is 1 of the 10 patients with bacterial endocarditis discharged from the hospital in a state of apparent arrest during 1 year. He is the only one in whom the infecting organism was the enterococcus. If he behaves in a manner like the other 9, there is good reason to hope that this state of apparent arrest may prove to be genuine and enduring. Other patients with enterococcus in the blood stream have more recently come under our care and it is hoped that more information may, in due course, be acquired in regard to this rather malignant malady.

Summary. 1. A man, aged 34, with known valvular disease of the heart since 1927, developed bacterial endocarditis late in 1943.

2. Repeated blood cultures were positive for *S. fecalis* and this organism was found to be rather resistant to bacteriostatic action of nearsphenamine, mapharsen, thiobismol and penicillin; very resistant to the sulfonamides and quite susceptible to enterococcus bacteriophage.

3. After a long course of treatment in which several of these anti-infectious agents were used, the disease appears to have been arrested.

THE USE OF A "MODIFIED GLOBIN" FROM HUMAN ERYTHROCYTES IN HYPOPROTEINEMIAS*

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THE importance of maintaining in patients a proper amount of circulating protein need not be emphasized at this time.¹ This problem is of particular importance in the preparation of patients for a surgical operation. In such patients, if a proper protein level is not maintained, certain complications may arise. Some of these complications, such as wound disruption, intestinal edema leading to obstruction, greater tendency to traumatic shock, have been sufficiently emphasized.² Others, however, such as edema of the lungs, susceptibility of liver to damage from infections, anesthesia,³ etc., have not received sufficient attention.

It is not the purpose of this paper to discuss such complications, but to outline briefly basic principles for the selection of proper means to correct hypoproteinemia and to present evidence showing that modified human globin³ may be advantageously used in many patients.

The use of globin in the treatment of hypoproteinemias is primarily suggested by the fact that plasma is not usually available in the quantity needed for the proper treatment of this type of patient. The utilization of discarded red cells for the production of globin would practically quadruple the available amount of protein for parenteral feeding from the same number of donations.

By hypoproteinemia is meant here a

status brought on by: (a) insufficient intake of proteins over a sufficiently long period of time; (b) excessive losses, or (c) improper production. This status is generally revealed by a diminished total circulating protein, and frequently by diminished concentration of plasma protein. It is presumably accompanied by lowered protein reserves. The clinical manifestations of hypoproteinemia are generally minimal and present only in the severest cases or under special conditions such as operative procedure, injudicious administration of crystalloids, etc. The cases of latent or clinically silent hypoproteinemias form a very important group, the detection of which is essential. For this purpose an accurate history of the patient's eating habits is very important.

The nitrogen balance studies alone do not offer a criterion to judge the status of hypoproteinemia, nor are they sufficient for evaluation of the adequacy of treatment. Along with other criteria, they are of great usefulness. Amongst these criteria, the determination of the total circulating protein is probably the most informative. The total circulating protein in our work has been calculated from the plasma protein concentration, determined by the Biuret method,⁴ and the total plasma volume determined by the T-1824 dye method.⁵

When considering the choice of means

* This paper is the 18th of a series on plasma and plasma substitutes from the Laboratory of Clinical Pathology of the Bryn Mawr Hospital. The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Bryn Mawr Hospital.

to correct hypoproteinemias, the following essential elements must be considered: (1) the severity of the hypoproteinemia; (2) the time that can be reasonably allowed for its correction; (3) the patient's general condition, with particular emphasis on the condition of the liver, kidneys and of the gastro-intestinal tract.

The patient with a mild to moderately severe hypoproteinemia but with unimpaired liver, kidney, and intestinal function offers no problem, unless the time element is very pressing. The oral route is alone satisfactory for these patients.

We are particularly concerned in this paper with the patient who has a severe hypoproteinemia, who is in a poor general state of health, and who must be prepared for an operation within as short a period of time as possible. A similar group is made up of patients who cannot be adequately fed by mouth, or who have impaired liver and/or kidney functions. These patients offer a difficult problem and require skillful handling. A classic example is the patient who is admitted to a hospital with intestinal obstruction, which has developed over a long period of time, causing progressive impairment of the nutrition, with lowering of the total circulating plasma proteins and presumably of the protein reserves. In this group of patients the oral route alone is generally inadequate to restore a proper plasma protein level and it is necessary to resort to parenteral feeding.

Human plasma and amino acid solutions prepared by digestion or hydrolysis of proteins are the only practical sources of nitrogen so far used intravenously. Modified human globin has been successfully used as a substitute for plasma in such patients. Some of the cases thus treated will be presented here.

Case Abstracts. CASE 1. M. Mc., a white male, aged 78, suffering from portal cirrhosis with ascites received a total of 2490 cc. of modified globin containing 79 gm. of protein over 10 days while on a standardized diet with low fat and high carbohydrate and protein intake. The total circulating pro-

teins rose from 166 gm. to 198 gm. during this period of time and the ascites decreased considerably, with a weight loss of 3.6 kg.

CASE 2. H. H., a colored male, aged 44, was admitted to the hospital Sept. 26, 1944 suffering from a duodenal ulcer with gastric retention. The patient was given nothing by mouth for 5 days, water, salt, glucose and vitamins being administered intravenously. After this period he was placed on a liquid diet with 14 hourly feedings, which were gradually increased to consist of what follows: 10 feedings of 90 cc. of milk with 30 cc. of cream; 4 feedings of 120 cc. of strained fruit juice with a total N intake of only 4 gm. daily. This régime was maintained for 11 days (Oct. 1 to Oct. 11), during which time the urinary output was fairly constant, and the patient was in a negative N balance (Fig. 1). From Oct. 12 to Oct. 17 inclusive, the patient, in addition to the diet mentioned above, received daily intravenously 600 cc. of globin solution containing a total of 3.2 gm. of N. During this period of time the patient's measured total circulating protein remained constant at a figure near the calculated normal, and generally maintained a slightly positive N balance. Upon withdrawal of the globin, the patient returned to a negative N balance.

This patient was operated upon on Oct. 20 and a subtotal gastrectomy was performed. On the 21st postoperative day, the patient was placed on a diet with a total caloric value of 2500 calories daily and a total N intake of 9.6 gm. With this diet the patient was in a slightly positive N balance (Fig. 2). For a period of 3 days, from Nov. 24 to Nov. 26 inclusive, globin solution with a total nitrogen content of 3.2 gm. was administered daily. During this period of time definitely more N was retained than on oral feeding alone.

CASE 3. J. B., a 52 year old white male, was admitted to the hospital Nov. 15, 1944 suffering from an inter-trochanteric fracture of the right femur. He appeared to be in a normal state of nutrition and was placed on a standard soft house diet with approximately 60 gm. of protein a day. This inadequate diet was maintained for approximately 2 months, at which time the patient became afebrile. He was then placed on a weighed diet consisting of: protein, 30 gm.; fats, 100 gm., carbohydrates, 295 gm. The total caloric intake was 2200 calories, and the

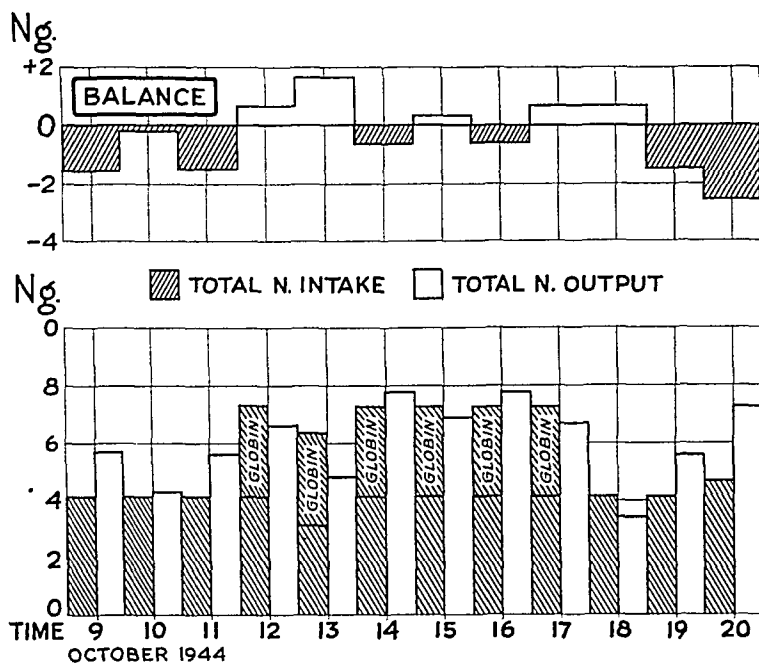


FIG. 1.—Nitrogen intake and output and balance in Case 2.

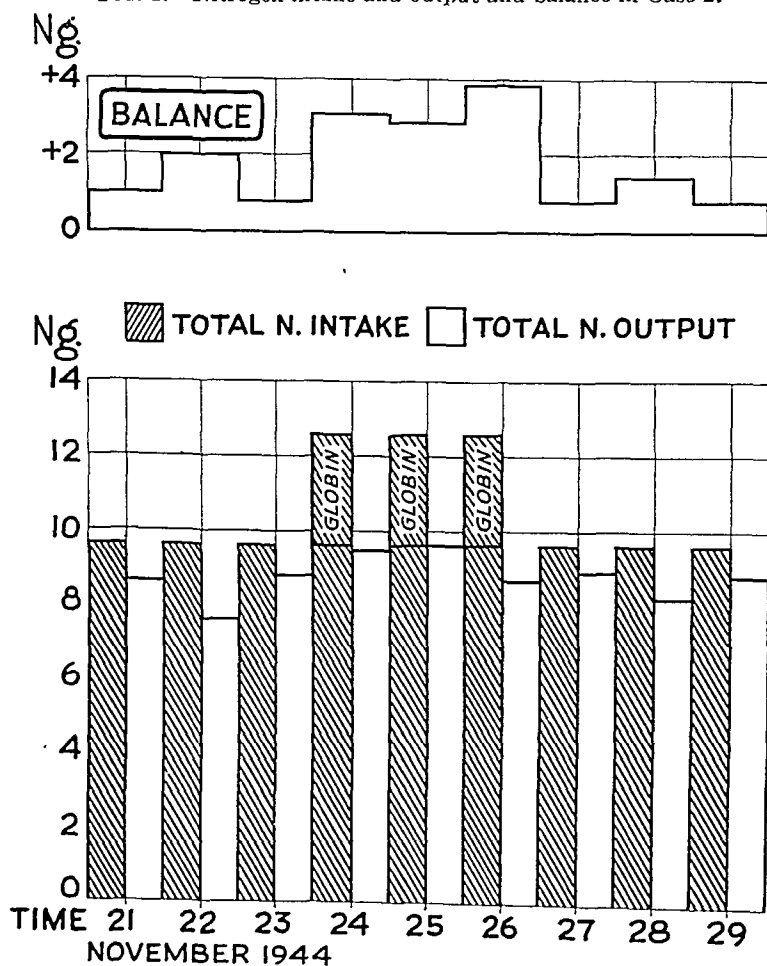


FIG. 2.—Case 2.

fluid intake was maintained constant at 2500 cc. per diem, which resulted in a fairly constant urinary output of about 1500 cc. daily. When intravenous feeding was given, the fluid intake by mouth was cut down accordingly. The results are shown in Figure 3.

It will be noted that the daily intravenous administration of globin solution containing 8.6 gm. of nitrogen caused a sharp reversal of the N balance, which became definitely positive. When the intravenous feeding was stopped the N balance became once again strongly negative. As a control, this experiment was repeated using orally globin and a casein hydrolysate (Casec). Similar results were obtained, although globin by mouth did not appear to be as effective as when administered intravenously.

that reported by Whipple in doubly depleted dogs.⁶

On the 4th day following the last of the intravenous injections of globin, the total circulating proteins were already declining.

CASE 4. R. B., a white woman, aged 59, suffering from carcinoma of the rectum extending into the vagina. Symptoms of bleeding had been present for over 1 year and during this period the patient lost approximately one-third of her total body weight. Prior to an abdominal perineal resection on March 21, the patient was given numerous whole blood transfusions in preparation for the operation. Following the operation, she was given crystalloids, plasma and globin as well as 200 cc. of packed resuspended erythrocytes, as shown in Figure 5.

During the 8-day period from March 23

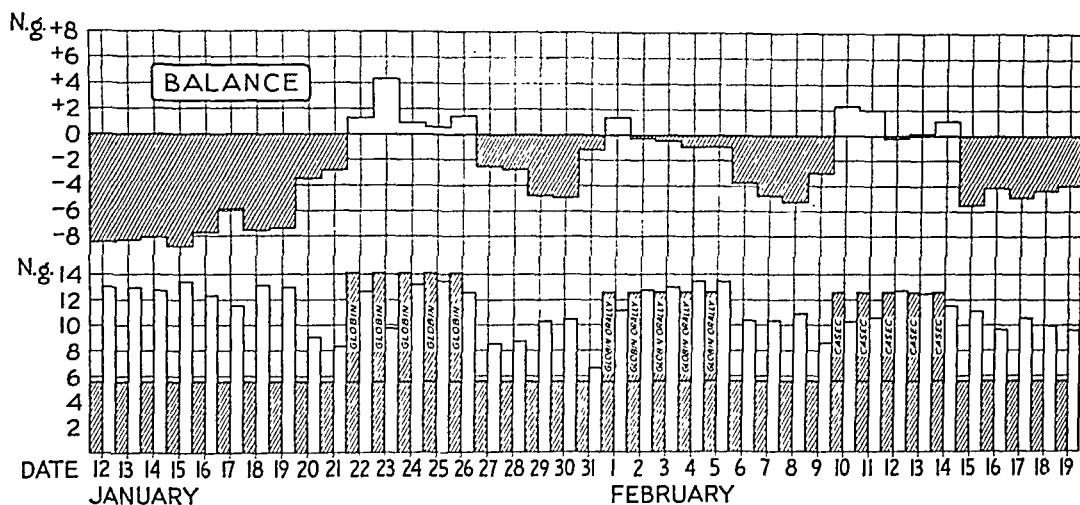


FIG. 3.—Case 3.

On a standard weighed diet with a N intake of 5.6 gm. a day, the determination of the total circulating protein, before the injection of globin was begun, gave a value of 219 gm. Upon the administration intravenously for 5 consecutive days of a globin solution with a daily content of 8.6 gm. of N, the plasma protein concentration remained the same (7 gm. before inoculation, 7.1 gm. after inoculation) but the total circulating proteins rose sharply to a peak of 309 gm. (Fig. 4).

The patient apparently utilized for the production of plasma protein alone 90 gm. of globin out of a total of 260 gm. injected or a ratio of better than 3:1. This represents a good utilization, somewhat better than

to March 30 inclusive, the patient received nothing by mouth. Intravenously she received 4200 cc. of globin solution containing 168 gm. of proteins and 3000 cc. of plasma containing a total of 170 gm. of protein. Before the intravenous feeding, the plasma protein concentration was 5 gm.%. On the 8th day, it was 6.1 gm.%. This patient was thereafter maintained on oral feeding and suffered a sharp drop in the plasma protein concentration, which was corrected by additional intravenous administrations of globin and plasma in the ratio of 3:1. The patient made a satisfactory recovery (Fig. 5).

CASE 5. E. D., a 69 year old white woman, was admitted to the hospital April 14, 1945, with complaint of nausea, vomiting, con-

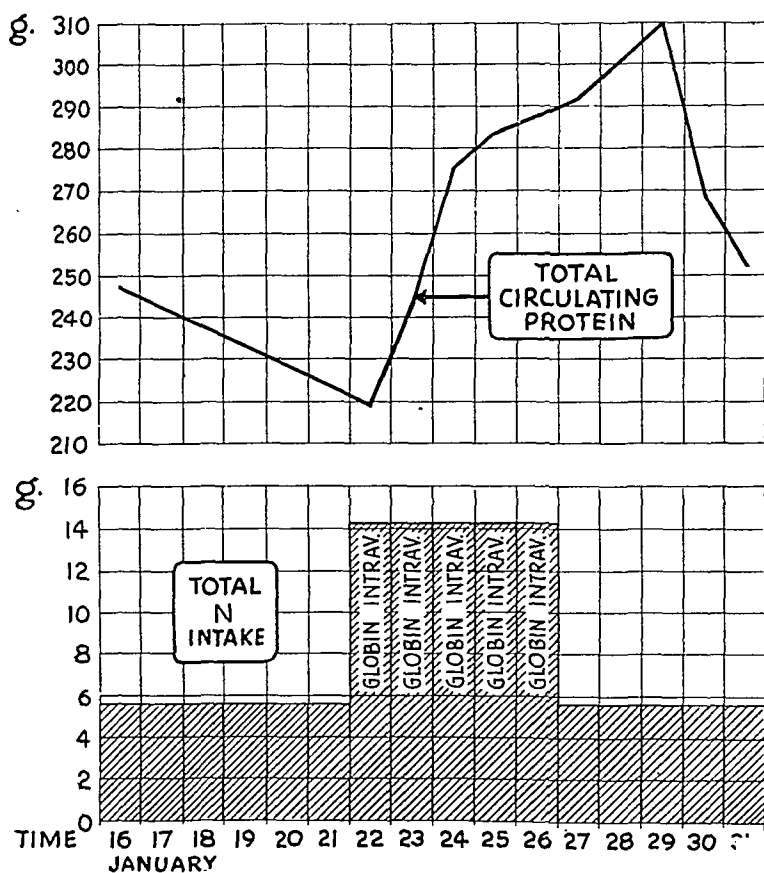


FIG. 4.—Case 3. Circulating protein and N intake.

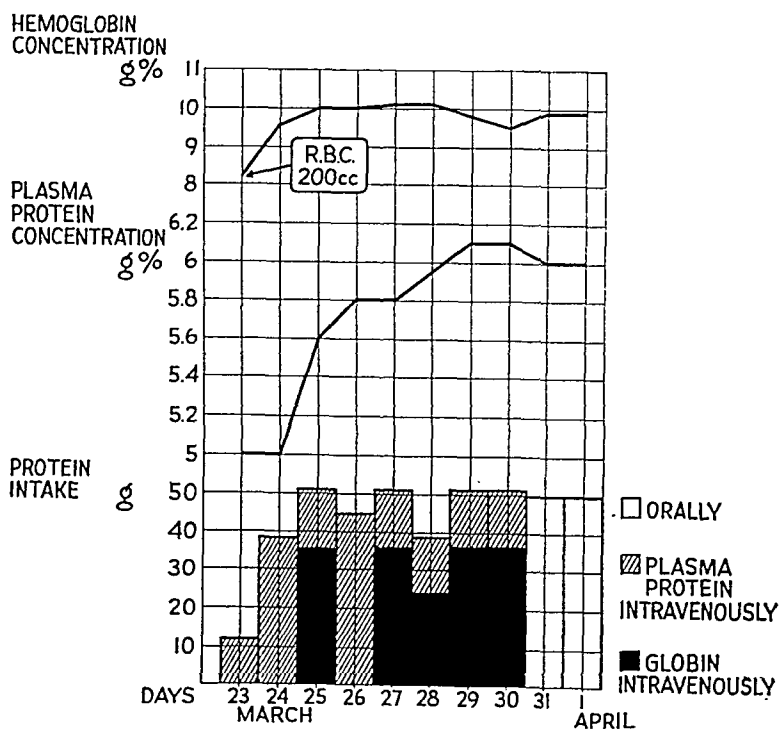


FIG. 5.—Case 4. Protein intake and hemoglobin and plasma protein concentration.

stipation, lower abdominal pain and occasional black stools. The abdominal pain had begun about 2 months before admission and vomiting 2 weeks before. The pain shifted to the epigastrium and for 2 weeks prior to admission the patient retained practically no food and little fluid. One week before admission, the bowels became obstipated, and 2 enemas gave no relief.

during this period. In the 3-day period while globin was administered, there was a good diuresis with a negative water balance resulting in the loss of 4680 cc.

During and following the administration of globin, the urinary N output remained constant. The plasma volume as determined by the dye method (T-1824) and daily hemoglobin determinations showed a sharp in-

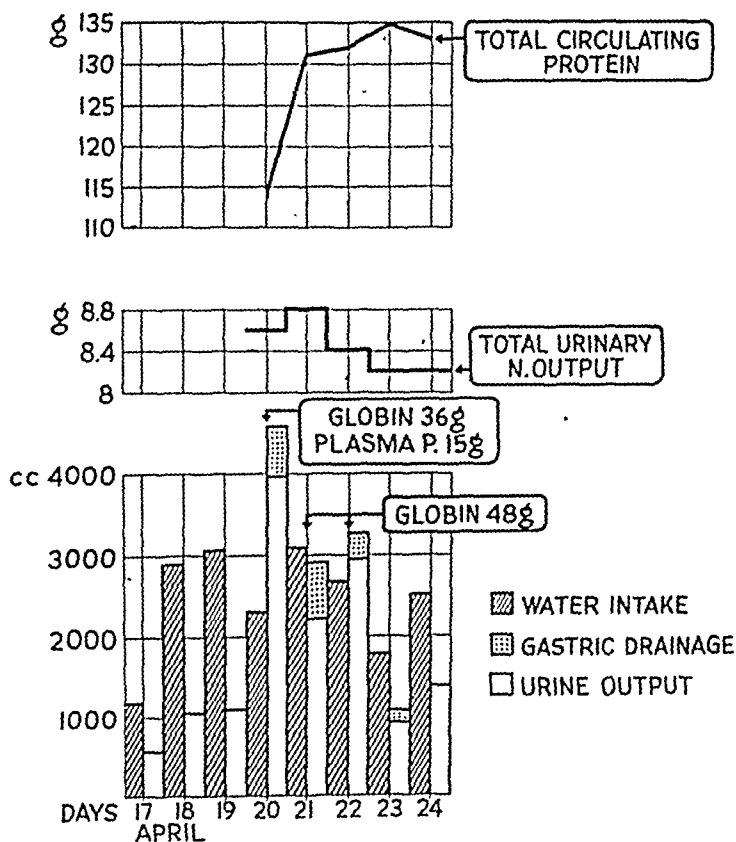


FIG. 6.—Case 5.

On admission the patient appeared dehydrated, and had no visible edema. The liver was palpable 2 fingers breadth below the costal margin and the urinary output was very scanty. Abdominal distention appeared the day following admission, while vomiting continued. The diagnosis of low intestinal obstruction was made, later confirmed at the operating table.

The hemoconcentration and hypochloremia existing on admission were corrected with the administration of 2% NaCl solution. During the 3 days preceding globin administration, there was a positive water balance. Allowing 700 cc. daily for insensible losses, the patient retained 2340 cc. of water

crease following the injection of globin. The total circulating proteins showed likewise a sharp sustained increase (Fig. 6).

CASE 6. C. G., a 53 year old white male, suffering from recurring gastric ulcer over a period of 10 years. He was first admitted to the hospital in Feb., 1944, at which time it was discovered that he had a fistula between the stomach and the gall bladder. On this occasion the patient received intravenously over a period of 40 days, 126 gm. of globin for the treatment of hypoproteinemia. He returned to the hospital in May, 1945 because of recurring gastric ulcer symptoms. His diet prior to admission had been poor. He was placed on a standard weighed diet,

“MODIFIED GLOBIN” FROM HUMAN ERYTHROCYTES

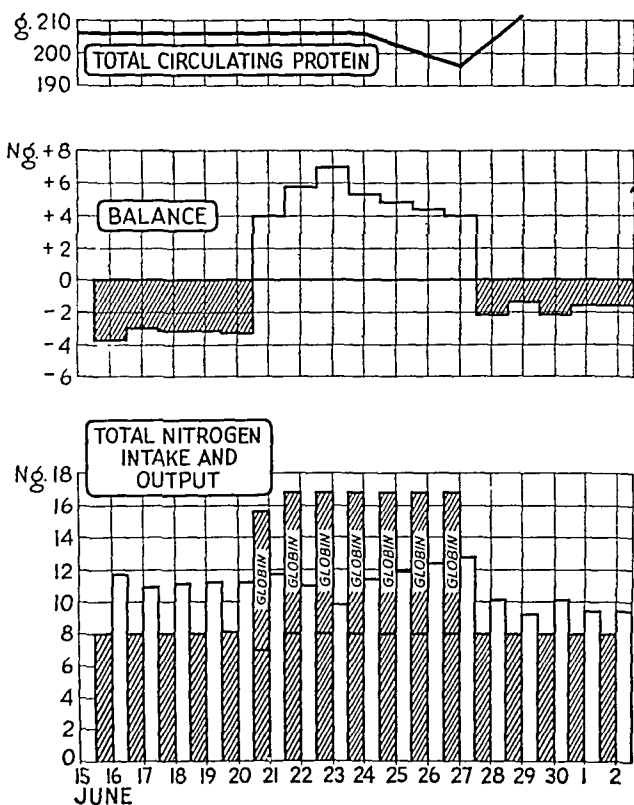


FIG. 7.—Case 6. Circulating protein, nitrogen intake, output and balance.

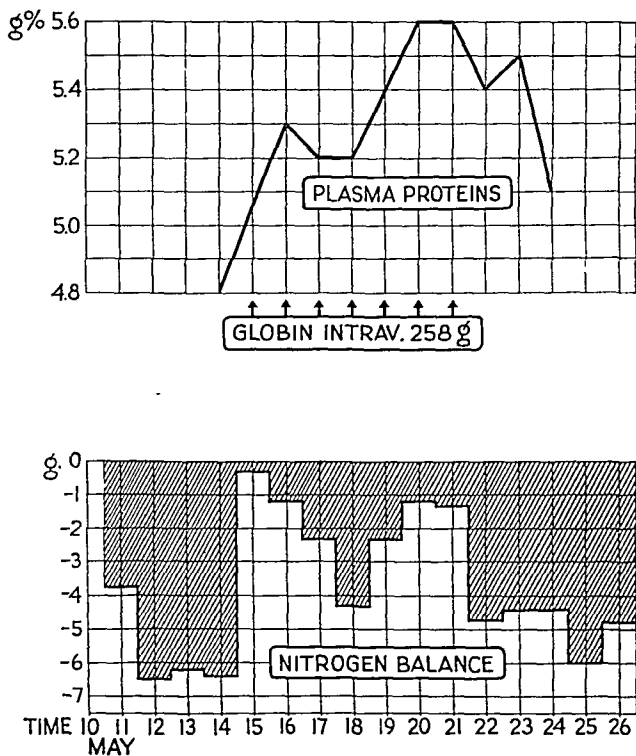


FIG. 8.—Case 7. Plasma protein and N balance.

containing 50 gm. of protein, 80 gm. of fat, and 307 gm. of carbohydrate. In addition, over a period of 7 days, the patient received a total of 370 gm. of globin intravenously. At the time of globin administration, this patient had a normal measured plasma volume and a normal plasma protein concentration. The total circulating protein remained constant at a level calculated normal for his weight and height (Fig. 7). The bulk of the injected globin was retained and apparently was stored as reserve, more exactly, of about 62 gm. of globin N about 18 were used to make up the deficit and most of the remaining were stored. A loss of about 2% of protein in the urine occurred during the globin injection.

CASE 7. F. J., a 34-year old white woman, was admitted to the hospital on April 6, 1945 this being her 6th admission. In 1937 she was admitted for treatment of numerous bullet wounds with penetration of the left chest, the stomach, the pancreas, the left kidney, the result of attempted suicide. At that time a mass in the cecal area was found. In 1939 she was operated upon for intestinal obstruction and the terminal ileum with the cecum and half of the colon were resected. The diagnosis of regional ileitis was made. Since that time the patient has suffered from severe hypoproteinemia, with recurring edema and on one occasion, intestinal obstruction.

On May 1, the patient was placed on a weighed diet, consisting of protein 45 gm., fat 70 gm., and carbohydrate 247 gm. With this diet the patient remained in a negative nitrogen balance. From May 15 to May 21, the patient received additionally daily intravenous injections of globin (Fig. 8) totaling 258 gm. Of this protein, the patient used slightly more than half to improve the N balance, although it remained negative; part was utilized to raise the plasma protein concentration from 4.8 to 5.6%. Lipemia prevented an exact estimation of the plasma volume and, consequently, of the total circulating proteins. During the period of observation there was a weight loss of 7 kg., the patient generally being in a negative water balance.

Summary of Cases. Case 1 shows globin utilization in a patient with severe liver damage.

Case 2 is one of severe hypoproteinemia

in which a positive N balance cannot be maintained by oral feeding. This is accomplished by additional intravenous globin feeding.

In the same patient, during late convalescence, and while in positive N balance, it is shown that the nitrogen balance can be made more strongly positive by additional intravenous globin feeding. It is presumed that in this patient the reserve proteins were still low.

Case 3 shows that in a patient with a severely negative N balance the bulk of globin N administered is retained and that the balance becomes positive. This is a patient with unquestionably lowered protein reserves. It emphasizes the value of globin in rapidly increasing the volume of circulating proteins in a bed-ridden patient with a low oral protein intake, high nitrogen losses and presumably much lowered plasma protein reserves. The rate of utilization is slightly more than 3:1 for plasma protein formation alone.

Case 4 shows how with plasma and globin a patient can be maintained in the postoperative period, when oral feeding cannot be adequately employed.

Case 5 emphasizes the value of globin in rapidly producing an increase in total circulating protein, with abundant diuresis, amounting to nearly 6 liters of urine in 3 days above the output prior to globin administration.

Case 6 shows that when the circulating plasma proteins are normal, the globin injected intravenously is used in part to make up the deficit in the N balance and the bulk of the remainder is stored.

Case 7 shows that when globin is administered intravenously to a hypoproteinemic patient maintained in a negative N balance, only part is utilized to make up the deficit in the N balance, while approximately half is utilized to regenerate plasma proteins in the circulating blood, the N balance remaining negative all the while.

Because amino acid solutions are somewhat less expensive and more readily available, they should be given the preference

over globin whenever possible.⁷ But amino acid solutions frequently give untoward reactions such as pains, vasomotor disturbances, and vascular thrombosis. These reactions can be controlled to a certain extent by reducing the concentration of the solution and decreasing the speed of administration.

A further limitation may be the inability of the patient with even a relatively minor impairment of the liver function to utilize amino acids for the synthesis of protein. Finally, patients with kidney lesions lose the major portion of the amino acids in the urine.

We have in addition noted, as have others^{2c,8} that in some hypoproteinemic patients, particularly if the hypoproteinemia is severe, amino acids are not well utilized. If utilization occurs in some of these patients, it represents only a small portion of the total N injected and requires a considerable period of time to produce an increase in the total circulating protein. The following case is typical of this group:

A colored adult male, suffering from duodenal ulcer with gastric retention, received a solution of amino acids* daily from Nov. 1 to Nov. 16 inclusive (1000 cc. of 10% solution intravenously daily or 100 gm. of amino acids containing 12 gm. of N). On Nov. 16, the 24 hour nitrogen output was 15.4 gm.; on the 17th, the day after the administration of Amigen had ceased, the nitrogen output in the 24 hour urine had dropped to 8.2 gm. For the next 5 days, on a constant nitrogen intake by mouth of 8.8 gm., the nitrogen output in the urine remained constant and averaged 8.1 gm. in 24 hours, or nearly 7.5 gm. less than the daily output while the patient was receiving Amigen. In other words, of the 12 gm. of nitrogen which the patient received intravenously daily, over 50% was excreted in the urine. During the 18 day period, in addition to the 12 gm. of nitrogen contained in the amino acid solution, the patient received nitrogen by mouth at a rate of about

4 gm. a day. Before the amino acid administration, the total plasma protein concentration was 5.3. After the completion of the administration of Amigen, the plasma protein concentration was 5.8%.

After a few days this same patient received for a period of 3 days globin intravenously, the dose containing 3 gm. of nitrogen daily. Oral intake of nitrogen at this time was about 9.4 gm. barely sufficient to maintain the patient on an even or slightly positive nitrogen balance. On Nov. 22, the plasma protein concentration was 5.3%. On the 30th, 4 days after discontinuance of the globin administration, it was 6.4 gm.%, the hemoglobin concentration having remained fairly constant during this period of time. Subsequent to the administration of globin, the patient received intravenously for 4 consecutive days 600 cc. of 5% amino acid solution (30 gm. of amino acids containing 3.6 gm. of nitrogen) while maintained in a slightly positive nitrogen balance by the constant oral administration of about 9.4 gm. of nitrogen per day. The additional intravenous feeding of amino acids did not increase the plasma protein concentration which was 6.4 before the amino acid administration and 6.3 after. During this period of time, the hemoglobin concentration remained constant. However, the amino acid administration again definitely increased the urinary nitrogen output. This patient did not have clinical evidence of hepatic insufficiency nor of renal lesion.

Discussion and Conclusions. Although plasma may be regarded physiologically and pharmacologically as the ideal material for intravenous nitrogenous feeding, it is difficult to obtain the quantity generally needed for the care of severely hypoproteinemic patients. Thus for the preoperative and postoperative care of a severely hypoproteinemic patient, who can take orally only a relatively small amount of food, a minimum of 700 gm. of protein intravenously are required as an average. In terms of citrated blood plasma with an average content of 5.5% of protein,

* Amigen, Mead Johnson Co., Evansville, Ind.

this means nearly 13 liters of plasma or about 53 donors. Often, as a compromise, plasma is used in quantity well below the optimal for intravenous nitrogenous feeding.

Of about 19 gm. of protein contained in 100 cc. of blood, only 3 gm. are utilized when plasma is separated and the red cell residue discarded. With the preparation of globin from the discarded cells, approximately 4 times as much protein can be made available from the same quantity of blood.

Plasma should be used preferably in those patients who, with or without hypoproteinemia, have disturbances which are aided by specific substances contained in the fresh or properly preserved plasma. This is particularly true of patients suffering from infection or hemorrhagic diseases.

Preliminary studies have shown that from the standpoint of nitrogenous intravenous feeding, modified globin can be adequately used to replace plasma. It has been our practice in these studies to use either globin alone or 1 part of plasma to 3 or 4 parts of globin. Our experience with amino acid solutions when compared with either plasma or globin is that it is decidedly less effective particularly in the severely hypoproteinemic patient and when time is limited. Amino acid solutions cannot be used in a patient with kidney damage or liver damage. Amino acids appear to be of benefit in maintaining a positive nitrogen balance in patients whose total circulating proteins and the protein reserves are not too low or have been raised by other means.

Whipple,⁶ in the doubly depleted dogs, has found that the utilization of modified human globin is good, there being produced during the period of injection about 35 gm. of hemoglobin and 24 gm. of plasma protein, the total injection being 168 gm., a ratio of approximately 3:1. This, notwithstanding the fact that the dog responds unfavorably to the administration of globin from human erythrocytes, and remains in a definitely negative N balance.

We have found that in the human definite increase in the circulating plasma protein and in the hemoglobin occurs upon administration of globin intravenously even when the nitrogen balance is negative (see Case 6). In the human, however, there is no reaction to the administration of globin to confuse the picture. In the human, the utilization of globin for plasma protein production is about 3:1.

We wish to emphasize the importance of maintaining the patients in a full caloric requirement, otherwise the utilization of globin or any other nitrogenous food for the production of plasma proteins is reduced.

In our studies in intravenous nitrogenous feeding with plasma, globin and amino acid solutions, we have been interested in the clinical response of the patient judged by the increased urinary output, increased volume of circulating blood, increased total circulating proteins, N balance, improvement in the clinical course such as amelioration of anemia, reduction of edema, etc.

We have been, however, particularly interested on the one hand in the relationship between intravenous nitrogenous plasma administration and the length of time in which an increased blood volume can be maintained and on the other hand, in the relationship between this time factor and the state of protein reserves.

The critical analysis of our results does not afford definite conclusions on this point.

However, it can be definitely concluded that plasma, globin and amino acid solutions do not have identical fields of clinical application, but that insofar as nitrogenous intravenous feeding is concerned, modified globin solution can be used adequately in place of plasma.

Modified globin can be used intravenously with good results even in the presence of severe hypoproteinemia, reduced plasma protein reserves, liver and kidney damage, conditions in which the use of amino acid solutions intravenously has been found to be of little or of no effect.*

* The authors have placed their conclusions with their discussion under a combined heading.

REFERENCES

1. STARE, F. J., and THORN, C. W.: J. Am. Med. Assn., **127**, 1120, 1945. LUND, C. C., and LEVENSON, S. M.: J. Am. Med. Assn., **128**, 95, 1945. LEVINE, S. Z.: J. Am. Med. Assn., **128**, 283, 1945.
2. THOMPSON, W. D., RAYDIN, I. S., and FRANK, I. L.: Arch. Surg., **36**, 500, 1938. JONES, C. M., and EATON, F. B.: Arch. Surg., **27**, 159, 1933. RAYDIN, I. S., STENGEL, A., JR., PRUSHANKIN, M.: and J. Am. Med. Assn., **114**, 107, 1940. ABBOTT, W. E., MELLORS, R. C., and MUNTWYLER, E.: Ann. Surg., **117**, 39, 1943. RAYDIN, I. S., McNAMEE, H. G., KAMHOLZ, J. H., and RHOADS, J. E.: Arch. Surg., **48**, 491, 1944.
3. STRUMIA, M. M., CHORNOCK, F. W., BLAKE, A. D., and KARR, W. G.: AM. J. MED. SCI., **209**, 436, 1945.
4. KINGSLEY, G. R.: J. Biol. Chem., **131**, 197, 1939; J. Lab. and Clin. Med., **27**, 840, 1942; J. Biol. Chem., **133**, 731, 1940.
5. GIBSON, J. G., JR., and EVANS, W. A., JR.: J. Clin. Invest., **16**, 301, 317, 1937; GIBSON, J. G., JR., and EVELYN, K. A.: J. Clin. Invest., **17**, 153, 1938. PRICE, P. B., and LONGMIRE, W. P.: Bull. Johns Hopkins Hosp., **71**, 51, 1942.
6. WHIPPLE, G. H.: Personal communication, June 19, 1945. See also: MILLER, L. L., ROBSCHT-ROBBINS, F. S., and WHIPPLE, G. H.: J. Exp. Med., **81**, 405, 1945.
7. LANDCOMAN, R., and WEINSTEIN, D.: Surg., Gynec. and Obst., **75**, 300, 1942. GARDNER, C. E., JR., TRENT, J. C.: Surg., Gyn. and Obst., **75**, 657, 1942. ELMAN, R., SACHAR, L. A., HOROWITZ, A., and WOLFF, H.: Arch. Surg., **44**, 1064, 1942.
8. Foreign Letters: J. Am. Med. Assn., **128**, 827, 1945.
9. MILLER, L. L., and WHIPPLE, G. H.: AM. J. MED. SCI., **199**, 204, 1940.

FATAL AGRANULOCYTOSIS WITH AUTOPSY FOLLOWING THE USE OF THIOURACIL IN A CASE OF THYROTOXICOSIS

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ALTHOUGH many cases of leukopenia and granulocytopenia complicating the administration of thiouracil in the treatment of thyrotoxicosis have been reported in the literature, only a very few fatal terminations as a result of the agranulocytosis are on record.^{1,2,3,4,5} As the use of this drug is still in its investigative stage, it is essential that the profession be advised of its dangerous potentialities. It is with this purpose in mind that we wish to add another fatal case of agranulocytosis following the administration of thiouracil for the treatment of thyrotoxicosis.

Case Report. H. S., 34, was admitted semistuporous on Sept. 6, 1944, at 12:04 A.M. Two days prior to admission, he had developed a sore throat, headache, general malaise and feverishness. The following day his condition grew worse. At 2 P.M. of that day he was seen by a physician. Because of the severe pharyngitis and fever, 102° F. sulfathiazole was prescribed. Five hours later, after he had taken 2 doses of the drug (30 gr.) his temperature rose to 105° F. He developed stupor and slight nuchal resistance. For the past 7 months he was under the care of one of us (M. G. W.) for the treatment of thyrotoxicosis.

On admission to the hospital, he was semistuporous with face flushed, markedly dyspneic, and obviously in acute distress. The temperature was 105° F., pulse 150, respiration 44. The eyes, ears and nose were essentially normal. The pharynx was markedly congested and covered in many areas with a glairy exudate. Slight nuchal rigidity was present. There was no cervical adenopathy. The thyroid was palpably enlarged and soft. The lungs were negative. The heart was rapid, normal in rhythm and not enlarged to percussion. A soft blowing mitral sys-

tolie murmur was audible. The abdomen was negative. Bilateral Babinski and Kernig reflexes were obtained.

A provisional diagnosis of meningococcal meningitis complicated by thyroid crisis was made and studies were immediately ordered. Lumbar puncture yielded a crystal clear fluid under increased pressure (260 to 270 mm. of water); a cell count of 27 W.B.C. predominantly neutrophils was reported. Although the physical appearance of the fluid was not in keeping with the diagnosis of meningococcal meningitis, penicillin was immediately administered intravenously at the rate of 300,000 units for the first 24 hours. Parenteral fluids consisting of 5% glucose in normal saline containing 1 dram of Lugol's solution in the first 1000 cc. was also immediately administered. Within 1 hour a hemogram was obtained which revealed a Hb. of 90% with W.B.C. 200 per c.mm. A stained smear revealed 50 lymphocytes only; platelets 200,000 per c.mm. and reticulocytes 0.7%. Because of the marked agranulocytosis the family was questioned further. It was disclosed that for the past 7 months he had been taking a new drug for his thyroid condition. This was verified as thiouracil by his private physician. The patient had presented himself at his office with a typical history of thyroid disease. B.M.R. was +32. Hemogram normal; blood sugar 102 mg. per 100 cc.; blood cholesterol of 180 mg. per 100 cc.; blood pressure 140/70. He was given thiouracil, 0.6 gm. daily, and within 2 weeks he gained 8 lbs. and the basal metabolic reading was found reduced to +19. Repeated white blood counts although normal indicated a slight reduction compared to the initial white count. At the end of 1 month of treatment, all the symptoms were relieved. He gained 24 lbs., his pulse was 80 and his B.M.R. was +14. The thyroid gland was perceptibly large. The widening of the

palpebral fissure was not decreased. He was maintained on 0.1 gm. of thiouracil 4 times daily. On June 8, his B.M.R. was +9. On August 12, he reported that, due to some domestic difficulties, he had undergone considerable mental strain. He had lost 13 lbs. His B.M.R. rose to +27; W.B.C. 5000 (60% neutrophils, 36% lymphocytes). Because of the low white blood count he was given 5 minims of Lugol's solution, t.i.d., in addition to the 0.4 gm. of thiouracil. Ten days later the patient telephoned Dr. Wohl and reported that he felt well and that he had gained 7 lbs. in weight. He was instructed to report for another blood examination, but failed to do so. According to the history obtained from a member of his family, he discontinued all medications of August 29.

It was obvious from what has preceded that we were dealing with agranulocytosis, most likely the result of the administration of thiouracil. Accordingly, in addition to the previously outlined régime the following were added: transfusion of 500 cc. of whole blood; pentonucleotide intramuscularly; leukocytic cream; crude liver; vitamins B and C in large doses; oxygen.

A repeated spinal fluid examination later in the afternoon of the same day revealed a lower pressure (not recorded in figures). A cell count of 3 W.B.C.; total protein 36.3 mg., sugar 77 mg., and chlorides 680 mg. Another hemogram revealed 250 W.B.C. per c.mm.; the differential count remained unchanged. A blood culture was sterile after 24 and 48 hours incubation. Urine contained trace of protein and 2 R.B.C. per H.P. field. Pharyngeal swab and culture revealed staphylococcus and diphtheroids, non-hemolytic streptococci.

His response to treatment was favorable toward the late afternoon of his 1st hospital day. The nuchal rigidity and Babinski reflexes disappeared. He responded to questions sluggishly but rationally. The irritability, however, as well as the restlessness persisted so that he had to be shackled. The pharyngeal exudates practically disappeared. No ulcerations were visible. On the following day, however, in spite of the continuation of the outlined régime he became more toxic and stuporous, sinking into deep coma. Temperature rose to 108° F., pulse and respiration in proportion. He expired at

4 A.M. on September 8 after a hospital stay of 52 hrs.

AUTOPSY. The pertinent findings were slight jaundice, prominence of the eyes, moderate pretibial edema. A moderately enlarged thyroid gland weighing 55 gm. The latter showed histologically areas of focal hyperplasia and focal colloid goiter (distended acini). The viscera showed evidence, grossly and microscopically, of shock. The slide of bone marrow was examined by Dr. Michael A. Rubenstein, Pathologist of the Montefiore Hospital, New York, who gave the following opinion: "The bone marrow is moderately hypoplastic, showing marked decrease of myeloid elements and a relative increase of nucleated red cells with appearance of younger forms of erythroblasts. The increase of red cell series is mainly an apparent one due to disappearance of the white cells." The brain could not be examined.

Comments. It appears clear from the clinical and pathological findings that our patient suffered from agranulocytosis resulting from the administration of thiouracil. Although he also received 30 gr. of sulfathiazole, his clinical symptoms and signs were manifest before the latter was given. Besides, there is to our knowledge no case on record in which the sulfonamides have produced an agranulocytosis in so small a dosage or in so short a period of time. Sulfathiazole was administered at 3 and 7 P.M. The hemogram was obtained 6 hours later.

We believe the agranulocytosis resulted in a lowered resistance to infection with subsequent production of a severe form of acute membranous pharyngitis. This infectious process, in turn, probably aggravated the hyperthyroid state which was complicated by a thyroid crisis which most likely contributed to the fatal termination. Although one may argue that the agranulocytosis could account for the above clinical course, the absence of any ulcerations after the complete disappearance of the pharyngeal membrane, the marked irritability, restlessness, and hyperkineticism during the entire course of his hospital stay, which required shackling

to restrain him even after the use of morphine and other sedatives and the high degree of pyrexia, are points in favor of a superimposed thyrotoxic crisis.

That the administration of thiouracil does not prevent a reactivation of thyrotoxic symptoms, is attested by the recurrence of this patient's symptoms, and by an elevated B.M.R. at the beginning of August 1944 in spite of the continuous intake of thiouracil since the middle of

treated with thiouracil—"even though the basal metabolic level was well within normal limits immediately before operation, there were upheavals of cardiac function and rises of body temperature after the operation, reminiscent of the patient operated upon with active hyperthyroidism."

It is also advisable to stress that agranulocytosis in this case became evident after what appeared to be a successful continu-



FIG. 1.—Thyroid glands showing areas of hyperplasia and colloid change.

February 1944. One of the cases reported by Paschis⁷ and his co-workers successfully prepared for thyroid surgery with thiouracil, died from thyroid crisis on the second day after a subtotal thyroidectomy.

Moore⁶ and his associates at the Thyroid Clinic of Massachusetts General Hospital, in a very exhaustive report on their observations on thiouracil, make the following statement: "It should be pointed out, however, that in a few patients"—

ous course of treatment with thiouracil for 6 months. In the case reported by Garcill and Lesses,³ the drug was administered for approximately 1 year. The dosage of thiouracil was relatively small, yet, there was a sudden explosive manifestation of agranulocytosis.

The histologic findings in the thyroid gland are of interest inasmuch as they present a dual picture, one of focal hyperplasia due to thiouracil, and another of

focal colloidal goiter as a result of iodine administration in conjunction with the thiouracil (Fig. 1).

The bone marrow findings (Fig. 2) account for the unusually abnormal hemographic findings—200 W.B.C. per cmm. is the lowest figure so far reported in the literature. Rubinstein⁸ reports a study of the bone marrow in a number of patients

The meningeal symptoms and signs were most probably evidences of meningeal irritation rather than of meningitis. The rapid disappearance of the meningeal signs as well as the rapid decrease of the spinal fluid pressure and the normal cytologic and chemical findings 8 hours after the initial lumbar puncture speak in favor of this opinion.



FIG. 2.—Bone marrow showing area of hypoplasia.

who developed agranulocytosis as a result of thiouracil and who recovered when the drug was withdrawn. He demonstrated an arrest of maturation associated with hypoplasia of the myeloid elements. Complete hematologic recovery followed the discontinuance of the drug. The return to normal of the bone marrow preceded that of the peripheral blood.

Summary. 1. A case of agranulocytosis resulting from the administration of thiouracil in the treatment of thyrotoxicosis is reported.

2. That the severe infections following the agranulocytosis may result in the reactivation of the thyrotoxic state and be complicated by a thyroid crisis, is stressed.

REFERENCES

1. ASTWOOD, E. B.: Treatment of Hyperthyroidism With Thiourea and Thiouracil, *J. Am. Med. Assn.*, **122**, 78, 1943.
2. FERRET, M. I., SPAIN, D. M., and CATCHCART, R. T.: Fatal Agranulocytosis Resulting From Thiouracil, *J. Am. Med. Assn.*, **127**, 646, 1945.

3. GARGILL, S. L., and LESSÈS, M. F.: Toxic Reactions to Thiouracil, *J. Am. Med. Assn.*, **127**, 890, 1945.
4. HIMSWORTH, H. P.: Fatal Agranulocytosis, *J. Am. Med. Assn.*, **125**, 1053, 1944.
5. KAHN, J., and STACK, R. P.: Fatal Case of Agranulocytosis Resulting From Thiouracil, *J. Am. Med. Assn.*, **125**, 358, 1944.
6. MOORE, F. D., SWEENEY, D. N., COPE, O., RAWSON, R. W., and MEANS, J. H.: The Use of Thiouracil in the Preparation of Patients With Hyperthyroidism for Thyroidectomy, *Ann. Surg.*, **120**, 152, 1944.
7. PASCHIS, K. E., CANTAROW, A., RAKOFF, A. E., WALDING, A. A., and TOURISH, W. J.: Thiourea and Thiouracil in Treatment of Thyrotoxicosis, *Endocrinology*, **4**, 179, 1944.
8. RUBINSTEIN, M. A.: Agranulocytosis Following Thiouracil Administration, *Am. J. Clin. Path.*, **14**, 544, 1944.

THE THERAPEUTIC VALUE OF EARLY PHYSICAL ACTIVITY IN RHEUMATIC FEVER

PRELIMINARY REPORT

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REST is the most universally accepted measure in the treatment of rheumatic fever. Rest has been advocated chiefly as a precaution to protect the already damaged heart, or to prevent or minimize its damage, either directly by decreasing the work of the heart, or indirectly in the belief that absolute bed confinement would shorten the illness and thereby reduce the incidence of cardiac involvement. The authors do not dispute the therapeutic value of rest, nor do they advocate an imprudent, negligent régime of early physical activity, particularly in the presence of prominent heart signs or even continuing tachycardia. On the contrary, this paper is an attempt to amplify the term "rest" and to emphasize the value of judicious physical activity as a component part of the therapy of rheumatic fever.

Confinement to bed has always implied the ultimate expression of rest, and as such has been the recommended treatment during acute rheumatic fever. Rest is a relative term. Rest and confinement to bed are by no means synonymous; restriction of physical activity is not necessarily rest. Rest, in our opinion, means maximum ease and comfort, physically, mentally, and emotionally. Bed rest ceases to be rest when the patient is no longer at optimum comfort in his environment. From that point this physical restriction should be termed bed confinement. Prolonged confinement defeats rest, produces restlessness, and thereby increased physical, mental and psychic activity. After prolonged restriction to bed, patients

become soma conscious. Symptoms unrelated to the disease assume serious proportions in the mind of the patient (and frequently in the mind of the doctor).

Based on our observations of more than 200 cases of rheumatic fever, it is our opinion that greater rest was obtained by permitting more freedom for activity, such as sitting in or out of bed, and walking to the latrine. Activities were permitted our patients during the acute phase of the disease, usually within the first 24 hours after admission, if their physical discomfort did not prohibit it. Rarely did joint discomfort prohibit ambulation for more than 48 hours when adequate amounts of salicylates were given. Regulated ambulation was permitted in the presence of any cardiac phenomena unattended by congestive failure. The patients were instructed to cease their activities before the appearance of dyspnea, fatigue, or other distressing symptoms. Tachycardia, cardiac murmurs, heart block, subcutaneous nodules, moderate joint pains, rapid sedimentation rates, abnormal electrocardiograms or other laboratory findings indicative of active rheumatic fever or carditis were not used as indications for bed rest or confinement. The patient's comfort alone was the determining factor regarding his bed status and physical activity.

Since the beginning of this study in May 1944, there has been no cause to regret this early physical activity procedure. There have been many favorable results, the most notable, perhaps, being the marked decrease of anxiety neuroses. To date, none of the patients has been

discharged from the service for this reason. On the contrary, these patients have slept more soundly and awakened more refreshed, and the energy expended by tossing and turning in bed has been minimized. Bowel habits have been regular; it has been rare to prescribe a laxative, cathartic, or enema. Consequently, the patients have enjoyed more abdominal comfort, and their better appetites have been reflected by gains in weight. There has been an increased feeling of well being. The morale for recovery has been excellent because the seed of apprehension of long or permanent invalidism has not been allowed to take root. The patient with psychic trauma often has proved more resistant to therapy than one with cardiac damage. The apathy, depression, and resignation effected by traditional therapy have been supplanted by the will to get well.

Management of Patient. *Method.* During the early stage of our program, patients frequently arrived at this hospital after the active phase of rheumatic fever had passed. The number of invalids as a result of cardiac neurosis was impressive. These patients were fearful of participation in any form of physical activity. To gain further insight concerning the cause of this fear, we instructed each patient to write his own history. He was encouraged to write everything which he had thought might have any relation to his illness—the cause, aggravating factors, preceding treatment, and questions regarding his personal prognosis. Our suspicions were confirmed: the fears were the result of the management of the patient rather than of the disease itself. We found that many of these patients had been confined to bed for months; that they had not been permitted to wash, shave, or feed themselves; that they had suffered all other restrictions enforced by a regimen of absolute bed rest; that they had been “listened to every day, blood tested, and electrocardiographed” frequently. In short, they had become the victims of medical science. The disease was cured

but the patient was lost. As a result of this well-intentioned management, the rheumatic fever was often replaced by an anxiety neurosis.

When a clinical estimate of the patient's mental and physical pattern had been achieved, management of physical activity was initiated. Appreciation of the severe degree of mental invalidism engendered by therapeutic programs demanding absolute bed rest throughout and beyond the clinical stages of rheumatic fever induced us to adopt certain modifications. Except in cases of heart failure and incapacitating joint inflammation, patients were encouraged to utilize the latrines during the acute stages of the illness. The patient's comfort, not the physical or laboratory findings, was the determining factor that influenced this judgment. Reference to case reports or graphic representations of the course of the disease cannot betray the willingness with which patients accepted latrine privileges, notwithstanding tender, swollen, and inflamed joints. As a rule, severe arthralgias were only of short duration before the full therapeutic effects of salicylates were realized. Such patients then were advised to avail themselves of the lavatory. It should be noted that the distance between the beds and the latrines was made as short as possible.

When the physical comfort had increased, the patient was permitted to sit in a chair for gradually increasing periods of time, provided that the limits of fatigability were not exceeded. As strength returned, ambulation was permitted about the ward and gradually encompassed visits to the ramp and the adjacent lawn. The continuation of the disease process, as revealed by elevated sedimentation rates, high white blood counts, shifts in the Weltman reaction or prolongation of the PR conduction times, was not considered a deterring element. The ward ambulatory stage of physical activity was abandoned, however, when, in the opinion of the observers, any recurrence of incapacitating or painful manifestations appeared. It was contrary to the purpose of the program

to effect any discomfort or pain. In the majority of cases the clinical and laboratory phenomena indicative of acute rheumatic processes diminished and disappeared during the period of physical activity. The patient was then allowed and encouraged to undertake simple handicraft tasks, permitted to leave the hospital on pass for short periods of time, visit other installations on the field when feasible, and attend Red Cross functions. Supervised picnics, overnight passes for the married men living within the confines of the adjacent city, and attendance at various courses under the direction of the military or allied authorities, were included in this stage of convalescence. In all the above phases of physical activity, full therapeutic doses of salicylates were prescribed.

The last phase of conditioning, consisting of graduated exercises, was ordered as the patients were considered fit according to standards established by the AAF Rheumatic Fever Convalescent Program.

Report of Cases. CASE 1. A 21 year old, white soldier, admitted Oct. 16, 1944, with a sore throat and migratory arthritis which involved the right thumb, both knees and the left second metatarsophalangeal joints. During the first 4 days of hospitalization, the temperature fluctuated between 100° F., and 103° F., and the pulse rate between 82 and 120 per minute. Further polyarticular migration involved the various joints of the hands, feet, knees, shoulders and left hip. A satisfactory joint response to salicylates was obtained within 24 hours. A systolic apical murmur appeared shortly after admission but was unattended by any objective or subjective evidence of cardiac or respiratory distress. Latrine privileges were permitted from the beginning of hospitalization and complete ward ambulation was undertaken within the 1st week. At the end of the 1st week the sedimentation rate (Westergren) reached 90 mm. per hour but declined thereafter. The leukocyte count did not exceed 7300, but variations in the amplitude of the T waves, particularly in the second and precordial leads, appeared in serial tracings. Omission of salicylate therapy at the end of

the 2nd week was followed by a recurrence of frank polyarthritis; the findings pertaining to the heart remained unaltered. Improvement again ensued upon salicylate administration and, in spite of an elevated sedimentation rate, an inconstant murmur, the indeterminate electrocardiographic changes, physical activity was undertaken in a graduated manner. The sedimentation rate returned to normal levels during the 4th week while the patient was ambulatory about the ward and the hospital grounds. The patient 6½ weeks after the onset of the illness voluntarily rode a bicycle 30 minutes without experiencing any distress or fatigue.

It is to be noted that while the patient increased his physical activity, the signs of acute and latent rheumatic processes diminished. Examination of the subject 6 months after the onset of the illness failed to disclose any cardiac or other abnormalities.

CASE 2. (Figures 1 and 2.) A 25 year old, white soldier, admitted April 21, 1944, with articular symptoms involving both feet, shoulders and elbows. At the age of 8 years he had polyarthritis which prevented activity for a period of 6 months. The temperature was 102.4° F. on admission, the pulse 108 per minute, and the white blood count 6600. A Grade 1 systolic murmur was heard to the left of the sternum and transmitted to the apex. Migratory symptoms affected the knees and ankles. Administration of sodium salicylate produced a rapid remission. The sedimentation rate declined from the previous level of 53 mm. per hour, but failed to return to normal. Reactivation was manifested by a secondary rise of the sedimentation rate, an invasion of the joints, and numerous crops of subcutaneous nodules of the hands, scalp and feet. The cardiac manifestations remained limited to the apical systolic murmur. Although the dosage of salicylates was increased, a left pleural effusion appeared. An apical diastolic murmur became audible during the 9th week, and basilar systolic and diastolic murmurs appeared during the 15th week. No signs of congestive failure could be detected at any time. For the first 16 weeks of hospitalization, the patient remained at absolute bed rest. Transfer to an area of low incidence of rheumatic fever was effected on the 17th week of the illness. On admission, the subject appeared acutely ill, the temperature was 102° F., and the pulse rate 146 per

minute. Bilateral pleural effusion, confirmed by roentgenograms, and apical systolic and diastolic murmurs were present. The cardiac silhouette and electrocardiographic tracings were normal on admission and throughout the hospital stay. The sedimentation rate was 68 mm. per hour; the white blood count was 7200, and numerous subcutaneous nodules were observed over the dorsa of the hands. Therapy with salicylates, sodium bicarbonate, magnesium carbonate, and, later, acetylsalicylic acid was prescribed.

the size and the number of subcutaneous nodules of the hands, a gain in weight, and a diminution of cardiac murmurs made their gradual appearance; only a persistent systolic murmur remained as residual cardiac evidence and at no time did the heart show any loss of reserve for ordinary ambulatory activity. The pleural effusion resolved completely and the sedimentation rate declined to normal in spite of progressively increased physical activity. In this case, the reactivation of the rheumatic process during the 25th

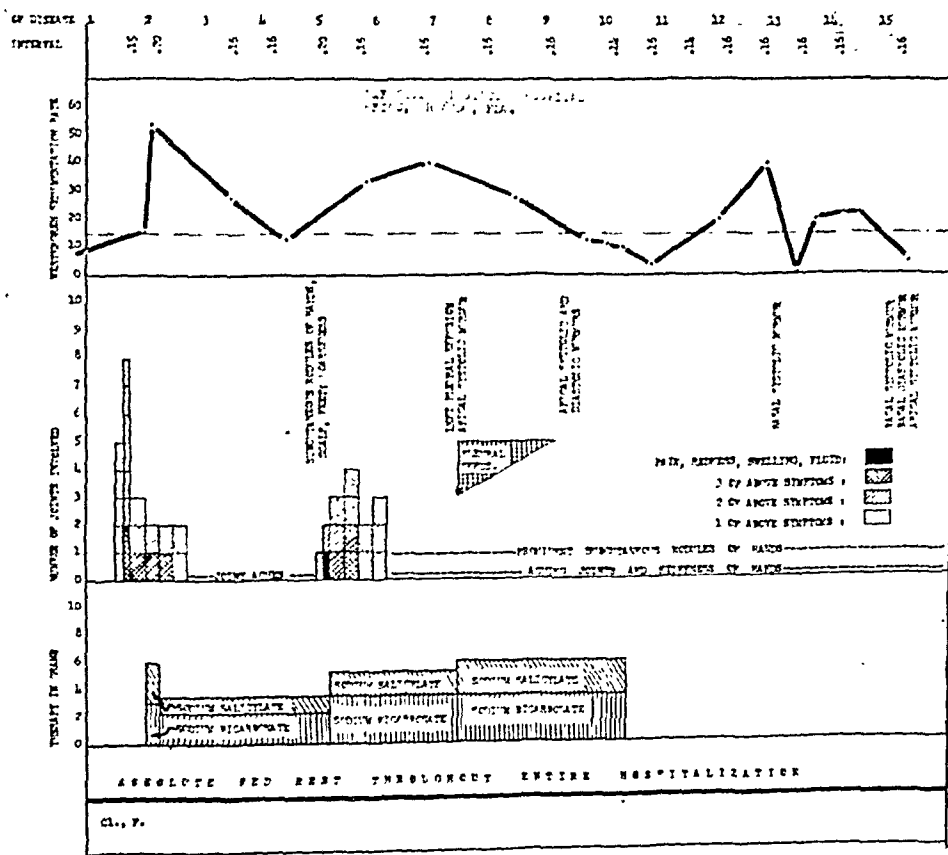


FIG. 1

Physical activity was permitted despite the acute manifestations. During the 25th week of the illness, when salicylate therapy was stopped, there appeared a recurrence of severe tachycardia, an elevation of the sedimentation rate, and a left pleural effusion. The response to readministration of salicylates was prompt. Physical activity was briefly limited by the patient's symptoms.

It is significant that the course of illness after the 17th week was attended by a decrease in the size of the heart. A decrease in

week of the illness can reasonably be attributed to the cessation of salicylate therapy and not to increased ambulation.

At the time of discharge a Grade 2 apical systolic murmur was the only recognizable evidence of cardiac damage. There was no indication of decreased cardiac reserve. The heart size and electrocardiographic tracings were normal.

CASE 3. (Figure 3.) A 24 year old, white soldier was hospitalized during the latter part of May 1944, for fever, sore throat, and

a cutaneous eruption, which was considered scarlet fever although peeling of the skin was not observed.

On July 2, 1944, he was readmitted for a nasopharyngitis followed in a few days by a migratory polyarthritis that involved the shoulders, knees, elbows and ankles. During the first 72 hours the maximum temperature was 101° F., and the maximum pulse rate was 94 per minute. The sedimentation

and subsequently subcutaneous nodules were found on the right hand and elbow. He lost 10 pounds during this period.

Transfer to this hospital was effected on Aug. 20, 1944, at which time the left knee was swollen. The temperature was 100° F., the pulse rate was 104 per minute, the leukocyte count and the electrocardiograms were normal. Salicylates (10 gm.) were given daily and latrine privileges granted in

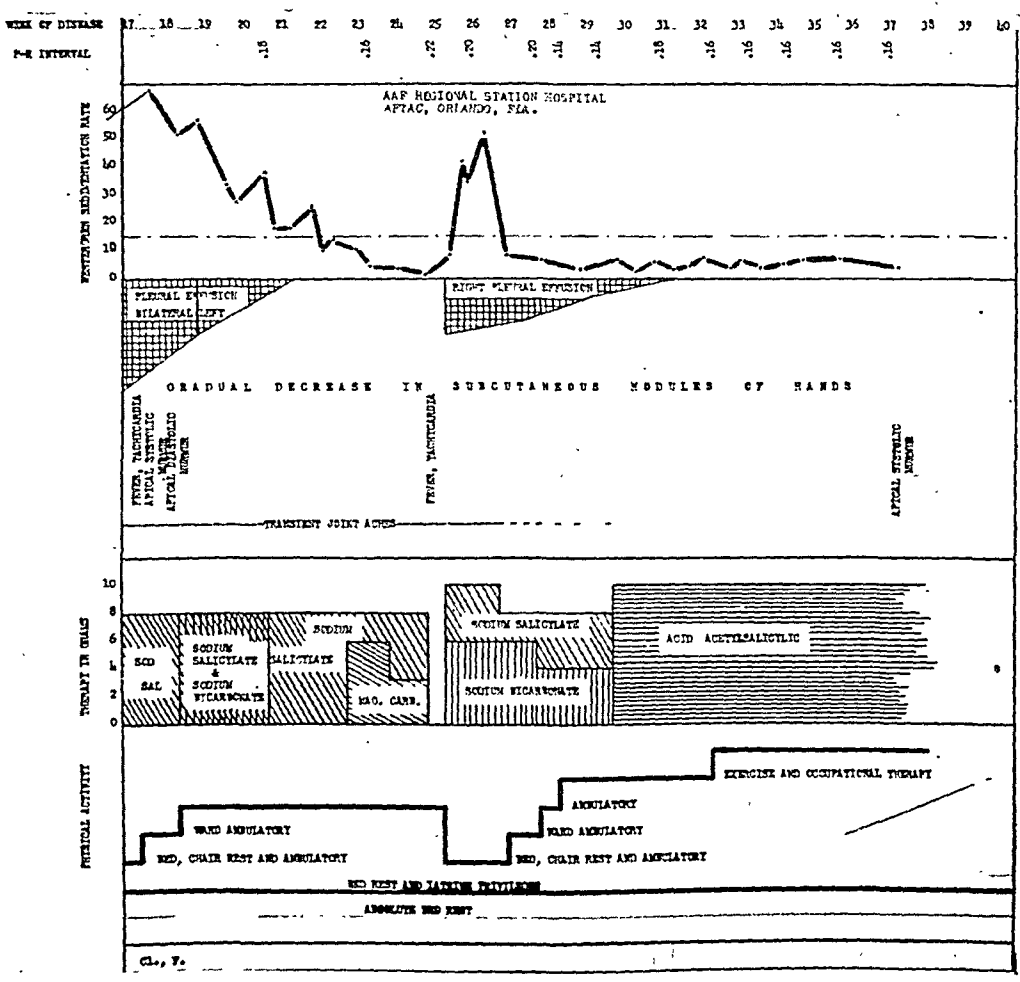


FIG. 2

rate was 54 mm. per hour and remained near that level during the first 6 weeks of absolute bed confinement. The white blood count was 9300, and other laboratory findings, including electrocardiograms, were normal. Administration of 6 gm. of sodium salicylate daily gave a satisfactory symptomatic response, but joint swellings persisted for 2 weeks. A constant apical systolic murmur became audible at the end of the 3rd week

spite of a mitral systolic murmur and elevated sedimentation rate of 79 mm. per hour. Although the patient's ambulation was increased in proportion to his physical comfort, the sedimentation rate declined satisfactorily, and both the murmur and subcutaneous nodules were gone after 7 weeks of ambulatory therapy. There was no recurrence after cessation of salicylate

therapy, and he regained his 10 pounds of lost weight.

The patient made an uneventful recovery, and completed the 6 phases of the AAF Rheumatic Fever Physical Training Program without interruption. He was discharged to

CASE 4. A 32 year old officer was admitted Aug. 26, 1944, 1 month following an acute tonsillitis. On admission, the patient was acutely ill with involvement of the heels, ankles, knees and shoulders to such a degree that turning in bed was impossible.

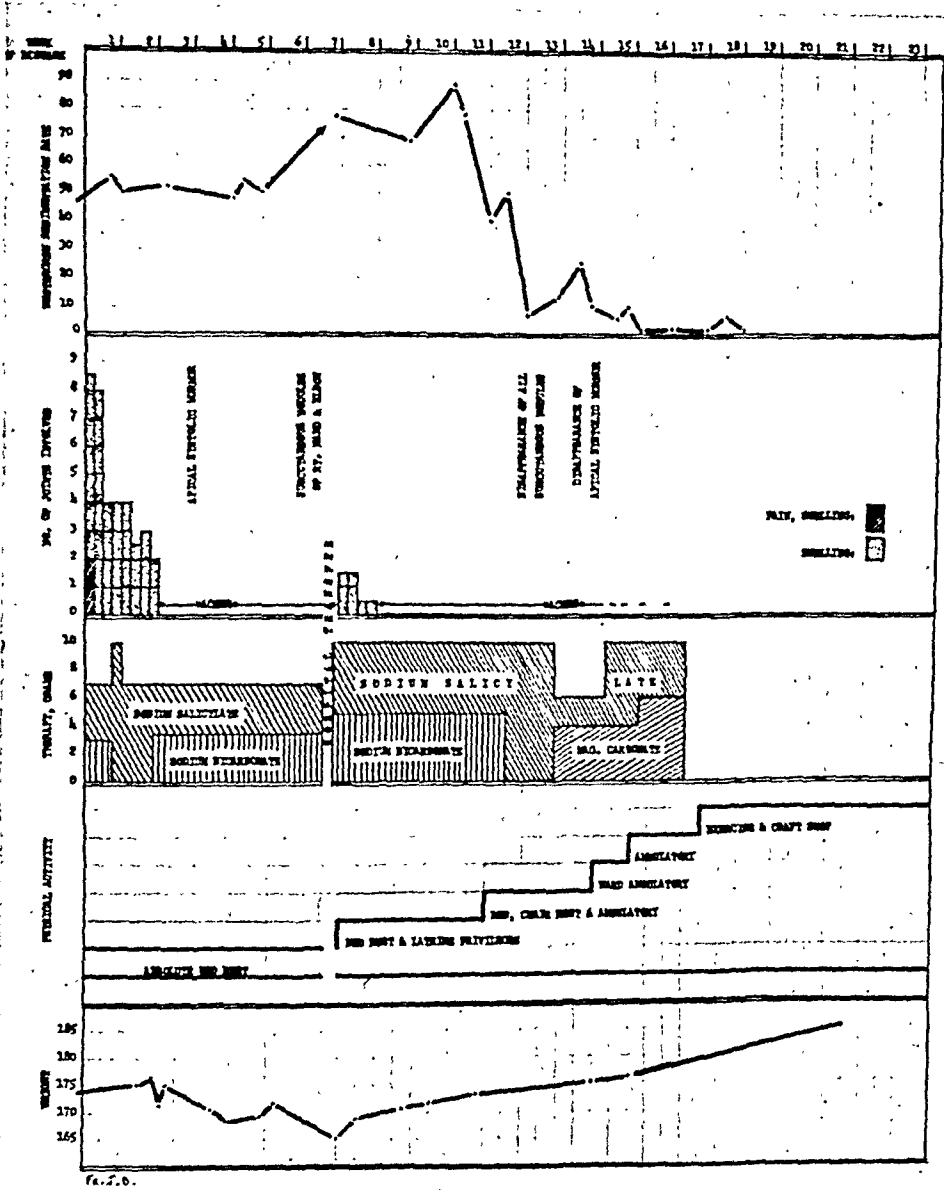


FIG. 3

duty without residua of rheumatic fever. It is worthy of note that increased physical activity did not prevent or postpone a complete recovery from the acute illness and did not produce any complications or permanent injury.

The tonsils were hypertrophic and acutely inflamed. After 24 hours, abdominal distention, dyspnea and cyanosis appeared, and additional joints became involved. Oral salicylates were stopped because of vomiting; the patient was critically ill and was placed

in an oxygen tent. On the 3rd hospital day there was a pericardial friction rub and physical signs of pneumonitis at the lower lobe of the right lung. On the 4th hospital day there was evidence of a pericardial effusion, a right pleural effusion, a diastolic gallop rhythm, slight edema of the ankles, and marked abdominal distention. Additional signs of circulatory failure were dyspnea, cyanosis, and venous congestion. The left cardiac border, by percussion, measured 14 cm. to the left of the mid-sternal line. Electrocardiograms showed sinus tachycardia with rate of 135 beats per minute, normal axis, low voltage of QRS complexes, large Q_3 (6 mm.), elevation of ST_1 , ST_2 , and inversion of T_3 . Subsequent electrocardiograms during the 1st month of the disease showed flattening of the T waves in the standard leads. There was no improvement in the patient's clinical condition until the use of intravenous sodium salicylates on the 14th hospital day. Within 24 hours there was an increase in the urinary output and a decrease in the abdominal distention. With the continued use of salicylates, the right pleural effusion rapidly disappeared and the pericardial effusion diminished. For one period of 24 hours when the patient did not receive salicylates there was a rapid return of joint phenomena. These responded promptly to the readministration of salicylates. On the 16th hospital day the patient was able to sit up in bed. From the 17th day of his illness the patient was allowed to sit in a chair in addition to latrine privileges.

The above phenomena occurred during the 1st month of illness. The temperature varied from 100° to 104° F. for 24 days. Laboratory findings during this period were: sedimentation rate varied from 70 to 105 mm. per hour; urea nitrogen (on admission) was 61 mg. %; electrocardiograms were consistent with pericardial effusion; and maximum white blood count was 18,300; bedside roentgenograms confirmed the diagnoses of pericardial effusion, right pneumonitis, and right and left pleural effusions.

The 2nd month of his illness was one of progressive improvement. The left pleural

effusion which developed about this time responded favorably, the pericardial effusion entirely disappeared, and the right pneumonitis was practically cleared by the end of the 2nd month.

From the 3rd month, all physical and laboratory findings, including electrocardiograms, returned to normal except for a moderate tachycardia. The occurrence of an acute nasopharyngitis on Oct. 9, 1944, was followed by 3 inflamed joints on October 15, which persisted for 2 days and responded promptly to salicylates. Since December 29, the patient progressed in the physical reconditioning program. Four months following discharge to duty, or 10 months after onset of illness, there were no sequelæ.

Summary and Conclusions. This paper is a preliminary report of observations made on 200 patients on whom the diagnosis of acute rheumatic fever was made by the clinical and laboratory criteria recommended by the Army Air Forces. From this study we have been impressed by two things: first, the high incidence of anxiety neuroses, often to a disabling degree; and second, the fact that prolonged bed rest was not necessary for an uncomplicated rapid recovery. Furthermore, early ambulation has greatly reduced the incidence and severity of the anxiety neuroses. The usual clinical and laboratory criteria for judging activity of the disease were not regarded as contraindications for starting early ambulation—the patient's physical comfort was the determining factor. Four case reports are included which illustrate our present program.

We recognize that this study does not warrant any dogmatic conclusions at this time; nor do we advocate indiscriminate physical activity. Nevertheless, it does invite attention to reevaluation of the currently accepted policy of prolonged bed rest, with its disadvantages, in the treatment of acute rheumatic fever.

THE RELATIONSHIP OF BLOOD PRESSURE AND SERUM THIOCYANATE

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THIOCYANATE (sometimes termed sulfocyanate) has been used as a hypotensive agent in patients with hypertension for more than forty years. Early workers, however, found it so highly dangerous that its use was virtually discontinued until Barker (1936)¹ repopularized it by pointing out the simple fact that serum levels could be used to determine the desirable level of dosage and to offset the dangers of overdosage. It has since been widely used and many reports of its clinical efficacy in suitable cases have appeared. The manner in which improvement is brought about by this drug in hypertensive subjects has not been clear. It has long been appreciated that thiocyanates are a normal constituent of the extracellular fluids. Nichols⁷ regarded the salivary glands as their chief site of formation. He considered that they were secreted into the saliva, swallowed and absorbed into the "system" appearing in tears and gastric juice. Sollman⁸ states "small quantities of thiocyanate are formed from the cyanide which arises in the metabolism of protein or which may be introduced in tobacco smoke or with vegetables such as succotash and onions. It is found in the blood and all body fluids in fairly equal concentration, about 0.03 to 0.06 mg. per 100 ml., and is excreted in the urine and feces, generally in the ratio of 1:2."

In 1942, Caviness and his associates^{3,4} reported studies on 241 persons who had never received thiocyanates therapeutically. They found blood serum levels ranging from 0.31 to 2.55 mg. per 100 ml. (estimated as potassium thiocyanate). Furthermore, they observed "... all

cases presenting high blood pressure fall in the low sulfocyanate concentration group; while in the high blood sulfocyanate group, no hypertension cases appear. Above a concentration of 1.54 mg. per 100 ml. no diastolic pressures above 90 mm. were found, and the only systolic pressures above 130 mm. were one of 150 mm. and one of 138 mm."

The conclusions drawn by Caviness are best stated in his own words: "This work shows that low blood pressure is associated with a high average blood sulfocyanate concentration, that high blood pressure is associated with a low average blood sulfocyanate concentration, and that borderline and normal pressure cases occupy intermediate positions; and it suggests very strongly, even if it does not prove, that sulfocyanates are nature's depressor substances which help to stabilize the balance between hypertension and hypotension."

More recently, Trasoff and Schneeberg⁹ reported a survey of 95 hospital in-patients in which the average value was 1.31 mg. KSCN per 100 ml. of blood serum (range 0.84 to 2.40). However, while these values agree closely with Caviness' study, no constant relationship between the height of the blood pressure and the level of the blood sulfocyanates could be demonstrated. Trasoff and Schneeberg concluded, "we cannot regard the blood sulfocyanates as naturally occurring depressor substances nor can we regard sulfocyanate therapy in hypertension as a form of substitution therapy for a substance that, because of a deficiency in the blood, has

allowed various pressor substances to act uninhibited. . . ."

It seemed important to us to decide which of these conflicting views were correct. Caviness' ideas, if acceptable, are basic to our understanding of the pathogenesis of hypertension, and he has advocated the therapeutic use of thiocyanates in small doses more or less prophylactically in the very earliest stages of asymptomatic hypertension. Accordingly, the following investigation was undertaken:

Method. Our survey covers 341 subjects composed of students from the 1944 freshman class of Queen's University, patients from the Ontario Mental Hospital, Kingston, in-patients at the Kingston General Hospital and patients from private practice. There were 268 males and 73 females; ages ranged from 16 to 84 years. Because of obvious sources of error, patients in cardiac decompensation, in shock, or suffering from myocardial infarction or febrile illnesses were excluded from the study. A mercury column sphygmomanometer was used for all blood pressure readings. With a few exceptions, these were made on the left arm with the subject in a supine position. Readings were repeated during the examination until the levels stabilized within a range of 4 mm. The systolic and diastolic pressures recorded are those of Phase I and Phase IV respectively.² Subsequently the blood specimen was taken for chemical analysis. No attempt was made to regulate the diet, smoking habits or physical activity of the subjects.

Technique. To 3 ml. of blood serum was added an equal volume of 10% trichloroacetic acid. This mixture was agitated thoroughly, allowed to stand 10 minutes, centrifuged for 20 minutes at 2000 r.p.m. and filtered. To 3 cc. of the protein-free filtrate were added 0.5 ml. of ferric chloride indicator and 6.5 ml. of distilled water. The resulting pinkish-yellow solution was then estimated in a Cenco-Sheard-Sanford photometer using a filter with maximum transmission of 400 μ . The accuracy of our work was checked periodically by recovery tests.

Results. The average value of serum potassium thiocyanate for the 341 cases studied was 0.79 mg. per 100 ml., with a range of 0 to 2.77 mg. per 100 ml. The

standard deviation of this group was 0.6 which means that two-thirds of the group fall within the interval 0.19 to 1.39 mg. per 100 ml.

Among 20 hypotensive subjects with an average pressure of 99/61 the average serum potassium thiocyanate concentration was 0.47 mg. per 100 ml. (range 0 to 1.21). Among 192 normotensive subjects, average pressure 120/69, the average serum concentration was 0.84 mg. per 100 ml. (range 0 to 2.77). In the borderline group, average blood pressure 137/74, 42 patients had an average serum level of 0.78 mg. per 100 ml. (range 0 to 2.10). In the hypertensive group, 66 subjects with an average blood pressure of 165/95 possessed an average thiocyanate value of 0.73 mg. per 100 ml. (range 0 to 2.20). In the group of 21 severe hypertensives whose average pressure was 228/131, the average thiocyanate concentration was 0.80 mg. per 100 ml. (range 0 to 2.10). The relationship of these diastolic blood pressures and serum potassium thiocyanate concentrations is shown graphically in Table 1.

(In plotting thiocyanate values against diastolic pressures, instead of against systolic pressures, we are following the precedent of Goldring and Chassis⁵ who believe an elevated diastolic pressure of more diagnostic significance in evaluating arterial hypertension than the systolic pressure. Actually, there was no essential difference in the appearance of our two graphs when systolic pressure was interchanged with diastolic pressure in constructing the ordinate.)

In this investigation of 341 subjects, the correlation coefficient of thiocyanate concentration and diastolic blood pressure was -0.13 , and the standard error 0.054. The square of the correlation coefficient was 0.017.

Discussion. A very slight inverse relationship is demonstrated between these two variables. However, the coefficient of -0.13 is practically mid-way between $+1$ and -1 , which signify perfect positive and negative correlation respectively, and zero which designates complete absence

TABLE 1.—AVERAGE VALUES OF GROUPS CLASSIFIED ACCORDING TO THE CRITERIA OF TRASOFF AND SCHNEEBERG

Group	No.	Blood pressure		Age	KSCN (mg per 100 ml.)
		Systolic	Diastolic		
1. Hypotension (below 106 systolic)	20	99.3	61.2	40.8	0.465
2. Normotension (107 to 130 systolic)	192	119.7	68.7	26.7	0.836
3. Borderline (131 to 140 systolic)	42	137.1	74.0	30.2	0.784
4. Hypertension (141 to 200 systolic)	66	164.9	95.0	45.0	0.727
5. Severe hypertension (over 200 systolic)	21	227.5	131.0	56.6	0.803

of correlation. Moreover, the coefficient of correlation must be squared to show the percentage of explained variation. This is 0.017, or an explained variation of less than 2%, which is so slight that it is insignificant. Indeed, it might be due quite as well to a normal sampling error as to a stable correlation.

Examination of the graph reveals a simple scatter distribution of data. This distribution resembles closely the results published by Caviness. Although the latter concluded that "the average blood sulfocyanate level for each blood pressure group varies inversely with the blood pressure," the graph of his results is so similar to ours that we believe it to be statistically insignificant also. If the correlation coefficient for his data were calculated, it is very doubtful that it would exceed -0.2 in magnitude.

The graphic picture of Caviness' findings conveys a false appearance of an inverse correlation because his graph is rectangular, not square, the abscissa or y-axis being almost twice the length of the ordinate or x-axis. This arrangement tends to cluster points along a regression curve sloping downwards from right to left. Furthermore, Caviness' two groups of hypotensive and borderline subjects are so small (9 and 19 at the prison and 10 and 12 at the State Hospital, respectively) that doubling or trebling the size of these groups might lead to a considerable shift in the averages calculated.

Although Trasoff and Schneeberg published no correlation coefficient, they concluded that there was "no constant relationship of blood pressure to blood sulfocyanate concentration." Our numerical results are parallel to theirs except that our average KSCN values are 0.3 to 0.6

mg. per 100 ml. lower. This could be due to having used a filter of different wavelength, 400μ as compared with theirs of 440μ . This variation in colorimeters probably explains the zero KSCN values among 47, or 14%, of our subjects.

It must be remembered, however, that the correlation coefficient is a measure of association only; in its interpretation association must not be confused with causation.⁶ Although two variables, A and B, may be associated, it does not follow that they are casually related, that a change in A is directly responsible for a change in B and *vice versa*. There may be some common factor, C, which is responsible for their associated movements. For instance, in a series of cities it might be shown that the tuberculosis death rate and overcrowding were correlated with one another. But this is not evidence that tuberculosis is due to overcrowding. Possibly, and probably, cities with a high degree of overcrowding are also those with a low standard of living. Such a third factor may be the one which is responsible for the level of the tuberculosis death rate, and overcrowding is only directly associated with it.

Finally, the statement that sulfocyanates occur "normally" in blood, made by both Caviness *et al.* and Trasoff and Schneeberg, should be challenged. They have assumed that the characteristic pinkish-yellow color reaction after the addition of an indicator, is due to the presence of thiocyanate as a ferric salt. This may well be the case, but an exhaustive search of the literature by us has failed to reveal any report of the isolation of a thiocyanate salt in crystalline form from either human or animal blood. Had our results supported Caviness'

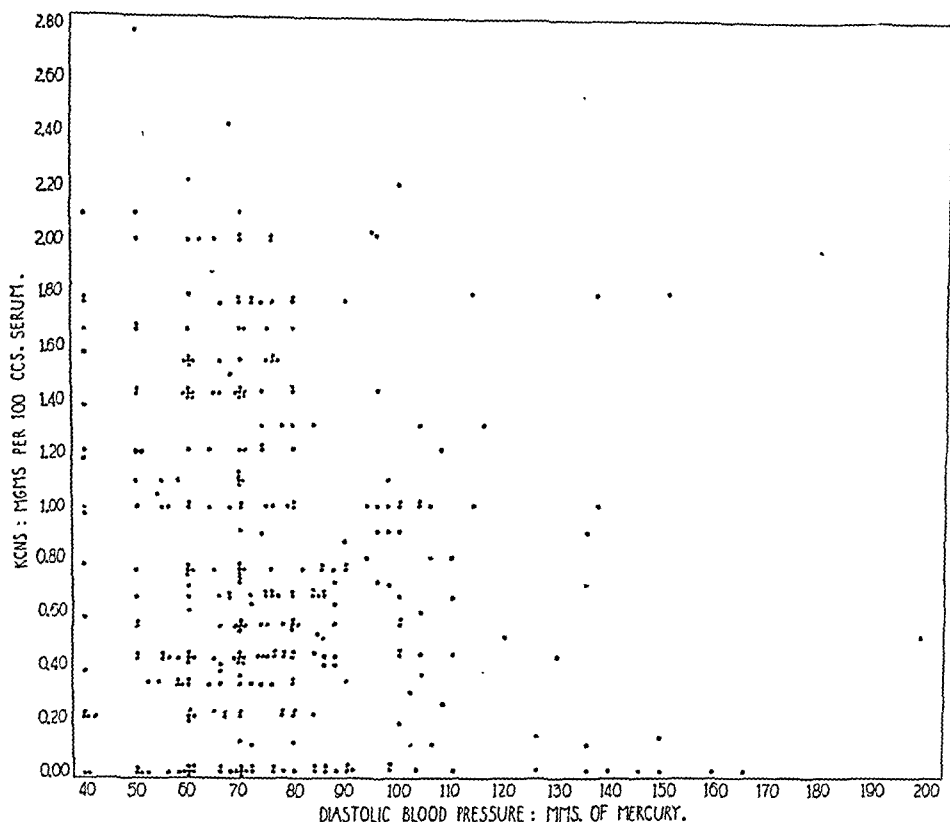


FIG. 1.—Graph of the relationship of diastolic blood pressure and serum potassium thiocyanate in mg. %.

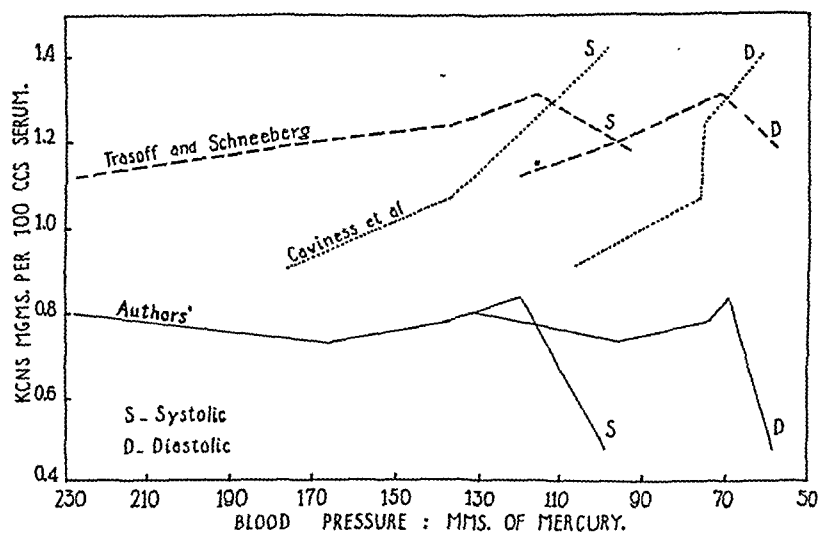


FIG. 2.—Graph comparing the findings of Trasoff and Schneeberg, Caviness *et al.*, and the authors concerning the relationship of blood pressure and serum potassium thiocyanate in mg. %. Each point represents the average blood pressure (systolic or diastolic) and the average serum potassium thiocyanate of a clinical group.

hypothesis of a negative correlation between blood pressure level and blood thiocyanate content, we considered attempting such isolation of a thiocyanate salt by fractional separation of the serum from ox or human blood. In view of our very definite findings of no correlation, we have decided against proceeding with this problem at this time.

Conclusions. 1. A substance, giving the color reactions of thiocyanate, was found to occur in the serum of 341 subjects, not

on thiocyanate therapy, in concentrations ranging from 0 to 2.77 mg. per 100 ml. (estimated as potassium thiocyanate).

2. There is no statistically significant relationship between the concentration of this substance and the diastolic blood pressure.

3. Our findings are definitely against the hypothesis that thiocyanate as found normally in human serum has any rôle in the regulation of blood pressure.

We wish to thank Messrs. H. Neuman and C. McIlveen for developing the laboratory technique and performing the thiocyanate estimations. This work was made possible by the Ontario Research Grant of Queen's University.

REFERENCES

1. BARKER, M. H.: *J. Am. Med. Assn.*, **106**, 762, 1936.
2. BEST, C. H., and TAYLOR, N. B.: *The Physiological Basis of Medical Practice*, Baltimore, Wm. Wood, p. 206, 1939.
3. CAVINESS, V. S., BELL, T. A., and SATTERFIELD, A. B.: *North Carolina Med. J.*, **2**, 585, 1941.
4. CAVINESS, V. S., UMPHLETT, T. L., and ROYSTER, C. L.: *AM. J. MED. SCI.*, **204**, 688, 1942.
5. GOLDRING, W. G., and CHASSIS, H.: *Hypertension and Hypertensive Disease*, London and New York, Oxford Univ. Press, p. 1, 1944.
6. HILL, A. B.: *The Principles of Medical Statistics*, London, The Lancet, Ltd., p. 106, 1937.
7. NICHOLS, J. B.: *AM. J. MED. SCI.*, **170**, 735, 1925.
8. SOLLMAN, T.: *A Manual of Pharmacology*, Philadelphia and London, Saunders, p. 987, 1942.
9. TRABOFF, A., and SCHNEEBERG, N. H.: *AM. J. MED. SCI.*, **207**, 63, 1944.

PALMAR ERYTHEMA—ITS RELATIONSHIP TO PROTEIN DEFICIENCY

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PALMAR erythema was apparently first distinctly described by Chalmers⁵ in 1899. Parkes Weber¹⁷ referred to this as "beer drinker's hands" in 1901. Interest was revived in 1929 when Lane¹⁰ described a familial variety of palmar erythema. Since then several reports have emphasized the coexistence and possible common etiological relationship between palmar erythema and cutaneous vascular "spiders."¹⁶

It is now well established that palmar erythema is not a rare clinical finding, and that it frequently is associated with pregnancy,^{1,6,11,16} cirrhosis of the liver ("liver palms"),^{4,12,13} pulmonary tuberculosis ("TB" hands"),¹⁵ rheumatoid arthritis, and a wide variety of other diseases.

The authors were impressed with the frequency with which palmar erythema was observed on all the wards of the William J. Seymour Hospital, Eloise, Michigan, particularly in diseases commonly associated with a protein deficiency.

During a period of 13 months (January 1942 to February 1943) 93 instances of palmar erythema were observed in examination of 1183 patients, an incidence of 7.9%. A similar incidence of palmar erythema has been observed in Salt Lake City by one of us (H. H.), while a lower incidence (about 5%) has been noted in Philadelphia (R. J.). The palmar erythema did not differ from that so adequately described by others,^{4,16} and often extended to involve the soft tissues of the entire terminal phalanx. Both the mottled and diffuse types were seen with occasional involvement of the soles. Cutaneous vascular "spiders" were frequently observed in these patients.

The ratio of male to female patients admitted to the Seymour Hospital, most of which are adults, is approximately 2 to 1. Children and pregnant women were not included in this study. Palmar erythema was evident in patients suffering from almost every type of disease (see Table 1) and in all age groups (17 to 90 years). It was observed in 2 colored female patients both with hypo-albuminemia, as well as in 3 apparently normal persons, 1 of whom had a hypo-albuminemia. In patients with hemiplegia or with a unilateral deformed hand secondary to rheumatoid arthritis the palmar erythema was usually more marked in the involved side.

The nitrogen determinations were made according to the method of Greenberg,⁷ and in 47 patients the total plasma protein concentration was checked with the gravity method of Barbour and Hamilton.² Globulin was precipitated out by the sodium sulfate method of Howe.⁸ The accuracy of the methods, reagents, etc., was established by determining the albumin and globulin concentration in the plasma of 47 samples of blood collected from 22 patients. Each sample was divided into two or three lots and each assigned new numbers. The chemist who made the analyses was unaware of the origin of the specimens. The variations in values for concentration of the plasma protein in the blood samples were as follows:

Day to day variations in the same patient if the concentration is approximately normal may be greater, but these variations are sometimes seen even with electrophoretic methods and therefore may be assumed to be physiologic.

* This work was done while the authors were on the staff of the William J. Seymour Hospital, Eloise, Mich.

† This work was supported in part by a grant from Frederick Stearns & Co., Detroit, Mich.

TABLE 1.—MAJOR DIAGNOSES OF PATIENTS SHOWING MARKED PALMAR ERYTHEMA

<i>Heart disease:</i>	Cor pulmonale	Myocardial infarction	
	Hypertension	Rheumatic valvulitis	
	Syphilitic aortitis	Subacute bacterial endocarditis	
<i>Arthritis:</i>	Rheumatoid	Mixed	
<i>Neurologic:</i>	Multiple sclerosis	Amyotrophic lateral sclerosis	
	Hemiplegia	Cord tumor	
<i>Psychosis:</i>	Organic	Functional	
<i>Genito-urinary:</i>	Stone	Neoplasm	
	Obstruction	Infection	
<i>Chronic osteomyelitis.</i>			
<i>Carcinoma:</i>	Gastro-intestinal tract	Face	Bladder
	Cervix	Lung	Kidney
<i>Chronic ulcers:</i>	Varicose	Decubitus	Peptic
<i>Burns.</i>			
<i>Endocrine:</i>	Diabetes	Obesity	Hyperthyroidism
<i>Cirrhosis of the liver.</i>			
<i>Blood:</i>	Anemia	Polycythemia	
<i>Vascular:</i>	Arteriosclerosis	Buerger's disease	
<i>Pulmonary:</i>	Pneumonitis	Bronchiectasis, tuberculosis	

TABLE 2.—VARIATION IN VALUES FOR CONCENTRATION OF THE PLASMA PROTEIN IN BLOOD SAMPLE

	Maximum variation	Average variation
Total protein, gm./100 cc.	0.7	0.26
Albumin, gm./100 cc.	0.7	0.25
Globulin, gm./100 cc.	1.2	0.31

The concentration of plasma protein was studied in 73 of the 93 patients. The data obtained from the palmar erythema group were compared with the usually accepted normal values and with those from a group of 40 unselected hospital patients. Three of the 40 control patients had photogenic palmar erythema confirming the over-all incidence of approximately 8%.

Hypoalbuminemia occurred more frequently in patients with palmar erythema (Fig. 1) than in the unselected group of patients. The concentration of albumin in the plasma in approximately 82% of the patients with palmar erythema was below 4.1 gm. per 100 cc. as compared to 62.5% of the unselected patients. Globulin values, as shown in Figure 2, do not deviate from the normal range as frequently as those for albumin. 33% of

the patients with palmar erythema and 10% of those in the unselected group show a concentration of globulin above normal, while only 5.5% of the former and 20% of the latter groups gave values below the normal range. This suggests that in patients with palmar erythema the concentration of plasma globulins tends to be increased while the plasma albumin is reduced.

The significance of the difference of the means between the incidence of hypoalbuminuria in patients with palmar erythema and the unselected hospital patients is indicated in Figure 3. As the difference between the two means is more than three times its standard error the chances are more than 99.7 in 100 that the difference is significant.

There is no significant difference between the total plasma protein concentra-

tion of the two groups even though the means of both groups are definitely below the accepted normal range. The albumin concentration in the plasma in the group with palmar erythema is not only below normal but the distribution around a slightly lower mean value is significantly different from that of the unselected group.

In 23 patients with palmar erythema the concentration of amino acid nitrogen in the plasma was found to be normal by the method used.⁹

While the authors wish to emphasize that approximately 80% of the patients with palmar erythema studied had hypoalbuminemia we do not suggest that protein deficiency is the cause of palmar erythema. Many patients with frank protein deficiency do not exhibit palmar erythema, and occasionally palmar erythema may exist in patients without demonstrable protein deficiency.

In only three^{4,11,12} of the twenty-one articles published on palmar erythema are

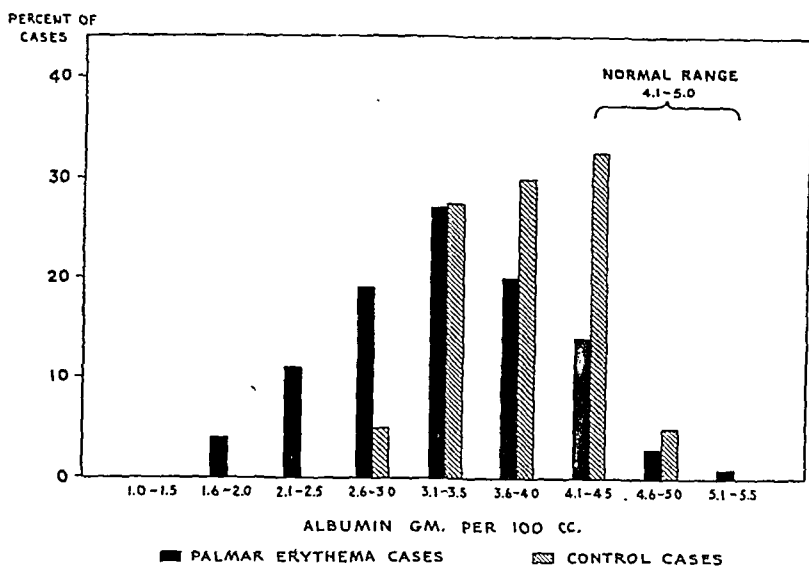


FIG. 1.—Plasma-albumin concentration in 73 patients with palmar erythema compared with 40 unselected patients in same hospital

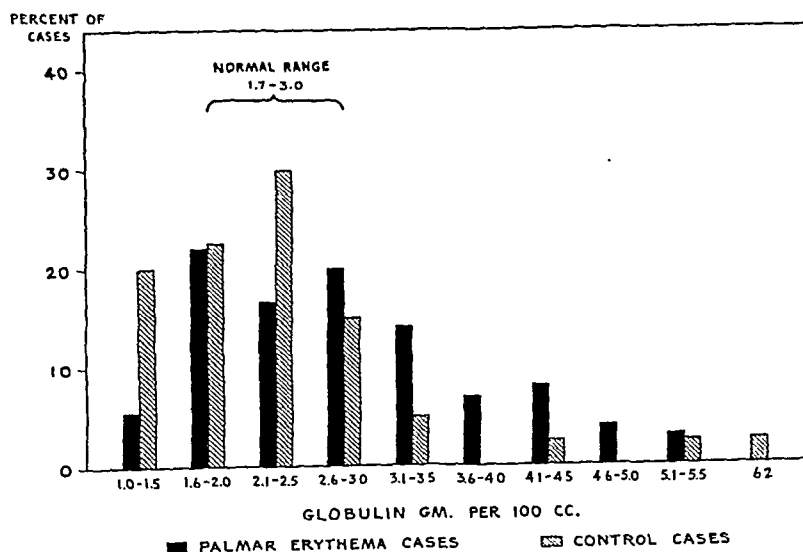


FIG. 2.—Plasma-globulin concentration in 73 patients with palmar erythema compared with 40 unselected patients in same hospital.

there any data given on the concentration of plasma proteins. Two^{4,11} give hypoproteinemic values in a total of 3 patients and the other¹² dismisses the question with a statement denying any consistent relationship in 14 cases but gives no data. However, the author does infer that a nutritional deficiency may be a factor.

It is noteworthy that the conditions or diseases in which palmar erythema frequently occurs also are known to exhibit a high incidence of protein deficiency. The incidence of protein deficiency in cirrhosis of the liver, pulmonary tuberculosis, and the latter half of pregnancy is

Lofgren¹¹ obtained questionable results following the administration of estradiol benzoate in 2 patients. Dr. A. Segaloff,¹⁴ who was at Eloise during this study, gave 4 patients 3 to 6 mg. of stilbestrol daily for several weeks. Two of the patients had cirrhosis of the liver, cutaneous vascular "spiders," impaired liver function, and slight palmar erythema. No increase in the palmar erythema was observed. The other 2 patients also had cirrhosis of the liver but did not have vascular "spiders" and no palmar erythema. Stilbestrol did not produce palmar erythema. A fifth patient with marked palmar ery-

	NO. CASES	TOTAL PROTEIN GM./100 CC.			STANDARD DEVIATION	STANDARD ERROR
		MIN.	MAX.	MEAN		
PALMAR ERYTHEMA	73	4.2	9.6	6.29	0.70	0.151
CONTROL GROUP	40	5.2	9.4	6.18	0.79	

DIFFERENCE OF MEANS 0.11

NOT SIGNIFICANT

	NO. CASES	ALBUMIN GM./100 CC.			STANDARD DEVIATION	STANDARD ERROR
		MIN.	MAX.	MEAN		
PALMAR ERYTHEMA	73	1.8	5.4	3.35	0.675	0.117
CONTROL GROUP	40	2.9	4.7	3.82	0.524	

DIFFERENCE OF MEANS 0.47

SIGNIFICANCE $\frac{0.47}{0.117} = 3.1$

FIG. 3.—Plasma-protein concentration in palmar erythema compared with control group.

greater than the reported incidence of palmar erythema in these conditions.

The erythema has been shown to be a result of dilatation of a comparatively rich supply of capillaries in the involved areas.^{1,16} At one time or another heredity,¹⁰ endocrine disturbances,^{4,11} chronic lung diseases,¹⁵ and nutritional deficiency,¹² have been offered as causative factors of palmar erythema. The adjacent arterioles may also be dilated. The skin covering the involved areas is of normal thickness and histologic structure.

While there has been one successful attempt to accentuate or produce palmar erythema by the injection of estrogens,³

thema, cirrhosis, impaired liver function, and hypoproteinemia was given 10 mg. of testosterone propionate per day for 10 days without any change in the palmar erythema.

Palmar erythema is due to a dilatation of the capillaries in richly supplied pads of the hands, fingers and feet. Once the erythema has become well established it usually does not completely disappear when the precipitating causative factor is removed. Palmar erythema appearing during pregnancy usually fades considerably during the postpartum period. In patients with cirrhosis of the liver the intensity of the erythema often decreases

perceptibly when the hypoalbuminemia is corrected and the hepatic function is increased. This suggests that the capillaries dilated under these conditions do not return to their previous normal state even though the dilating agent has been removed.

Impaired liver function is commonly found in patients with hypoalbuminemia. Bean³ suggests that abnormal metabolism of the 17-ketosteroid hormones may be a causative factor.

Palmar erythema has been observed to occur with equal incidence in both sexes and to have been present at birth and in the 10th decade. While the evidence indicates that the accumulation of excessive amounts of estrogens or 17-ketosteroids in the circulation either because of overproduction or decreased destruction by a poorly functioning liver can cause a sufficient capillary dilatation to result in palmar erythema it does not preclude the

possibility of other as yet unknown mechanisms.

Palmar erythema is usually symptomless and does not affect the patients adversely except for its possible conspicuous appearance. Nevertheless, if its true etiology was understood it might have considerable diagnostic significance.

Conclusions. Palmar erythema was observed in 93 of 1183 patients examined.

Palmar erythema occurred in all ages of both sexes studied and in a wide variety of diseases.

Hypoalbuminemia occurred in 83% of the patients with palmar erythema and in 62.5% of an unselected group of patients in the same hospital. This difference is significant.

Hypoalbuminemia is not regarded as cause of palmar erythema; but the finding of palmar erythema in a patient should suggest the probable existence of a protein deficiency.

REFERENCES

1. BAER, J. L., and REIS, R. A.: *J. Am. Med. Assn.*, **82**, 526, 1924.
2. BARBOUR, H. G., and HAMILTON, W. F.: *J. Biol. Chem.*, **69**, 625, 1926.
3. BEAN, W. B.: *Am. J. Med. Sci.*, **204**, 251, 1942.
4. BEAN, W. B.: *Am. Heart J.*, **25**, 463, 1943.
5. CHALMERS, H. J.: *Lancet*, **2**, 1514, 1899.
6. FELDMAN, S.: *Arch. Dermat. and Syph.*, **39**, 784, 1939; **40**, 1024, 1939.
7. GREENBERG, D. M.: *J. Biol. Chem.*, **82**, 545, 1929.
8. HOWE, P. E.: *J. Biol. Chem.*, **49**, 109, 1921.
9. KRAUEL, K. K.: *J. Lab. and Clin. Med.*, **29**, 222, 1944.
10. LANE, J. E.: *Arch. Dermat. and Syph.*, **20**, 445, 1929.
11. LOFGREN, R. C.: *Arch. Dermat. and Syph.*, **47**, 503, 1942.
12. PERERA, G. A.: *J. Am. Med. Assn.*, **119**, 1417, 1942.
13. RETNOFF, O. S., and PATEK, A. J., JR.: *Medicine*, **21**, 207, 1942.
14. SEGALOFF, A.: Personal communication.
15. TROSTLER, L. S.: *Am. Rev. Tuberc.*, **47**, 168, 1943.
16. WALSH, E. N., and BECKER, S. W.: *Arch. Dermat. and Syph.*, **44**, 616, 1944.
17. WEBER, F. P.: *Brit. J. Dermat.*, **26**, 165, 1914.

A SIMPLIFIED APPARATUS FOR THE INDUCTION OF ARTIFICIAL PNEUMOPERITONEUM

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In a previous article¹ the great utility of this simple diagnostic procedure was discussed, and the use of the Robinson pneumothorax apparatus to induce a pneumoperitoneum was described. Attention was invited to the fact that this afforded the simplest and safest method available:—

1. To determine the presence, position, size, contour, mobility, and attachments of certain abdominal organs (particularly the liver, spleen, stomach and kidneys).

has failed to show a single instance of this serious complication having occurred with the use of carbon dioxide. Experimental evidence supports the contention that this gas is safe.²

The technique of inducing artificial pneumoperitoneum has since been further simplified so that it can be performed in the office, clinic, or Roentgen ray department. The use of the Robinson pneumothorax apparatus has been discontinued in favor of a home-made system, which

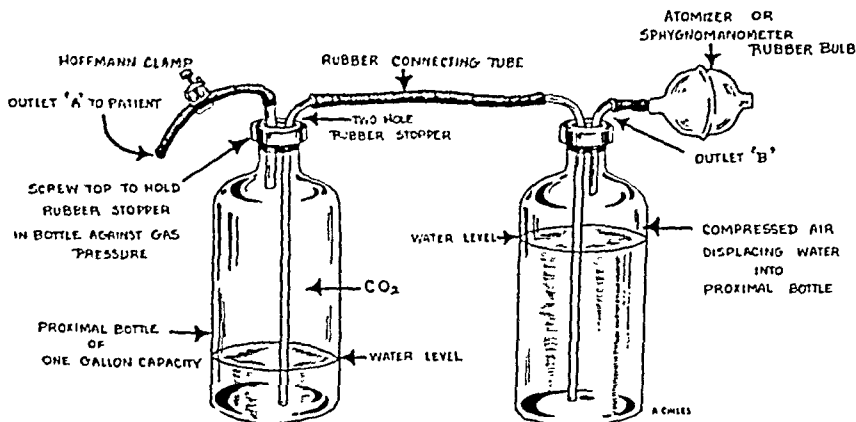


FIG. 1

2. Preliminary to splenectomy, so as to forewarn the surgeon as to whether this organ be adherent, etc.

3. To differentiate between intraperitoneal and extraperitoneal rupture of the urinary bladder.

4. To demonstrate intra-abdominal adhesions.

5. To outline the subdiaphragmatic spaces.

6. In the treatment of tuberculous peritonitis.

It was pointed out that since carbon dioxide had been substituted for air, as the gaseous contrast medium, the danger of gas embolism had probably been eliminated. A follow-up study of this point

has the advantage of greater economy and greater gas capacity. With the former, adequate visualization in patients who had had an ascites of a considerable degree, required the delay and inconvenience of refilling the bottles in order to administer amounts greater than 2000 cc. of carbon dioxide.

The assembly is illustrated in Figures 1 and 2. Initially, the proximal bottle is filled with water. Outlet "A" is attached to a tank of carbon dioxide, the atomizer bulb is disconnected from outlet "B" and the gas turned on. This displaces the water from the proximal bottle over into the distal one, and leaves the former filled with carbon dioxide gas. Outlet "A" is

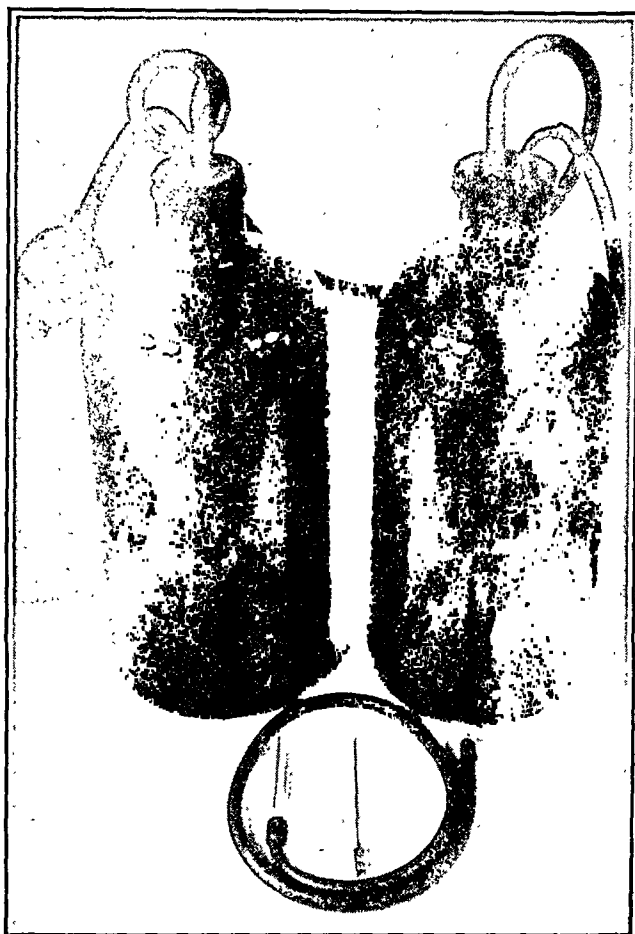


FIG. 2.—Showing how the screw caps to the bottles have been cut out to permit passage of inlet and outlet tubes at the same time preventing pressure within the bottles from blowing out the rubber stoppers. The only part of the unit requiring sterilization is shown at the bottom of the plate.

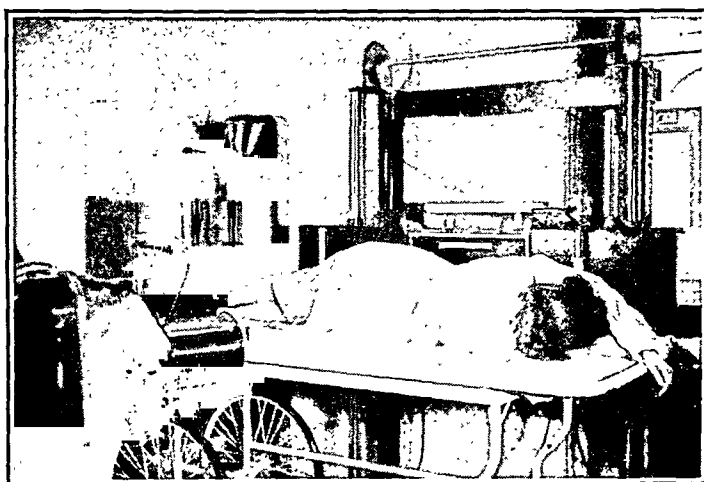


FIG. 3.—The patient lies with right side down in order to visualize the spleen.

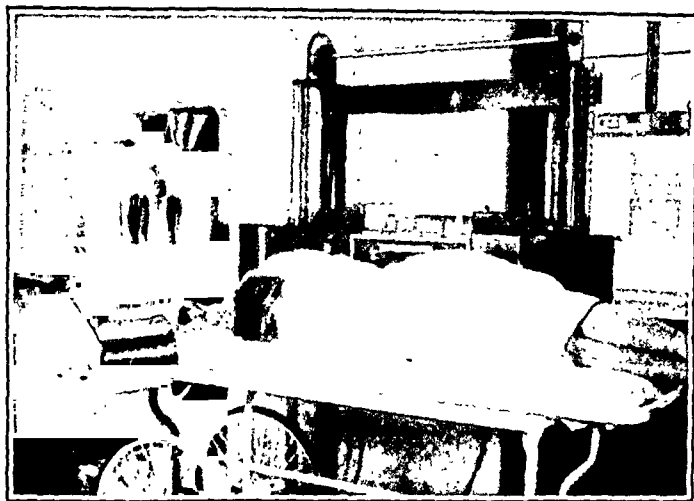


FIG. 4.—The patient lies with left side down in order to visualize the liver



FIG. 5.—The subdiaphragmatic spaces are visualized by exposing the film with patient standing.

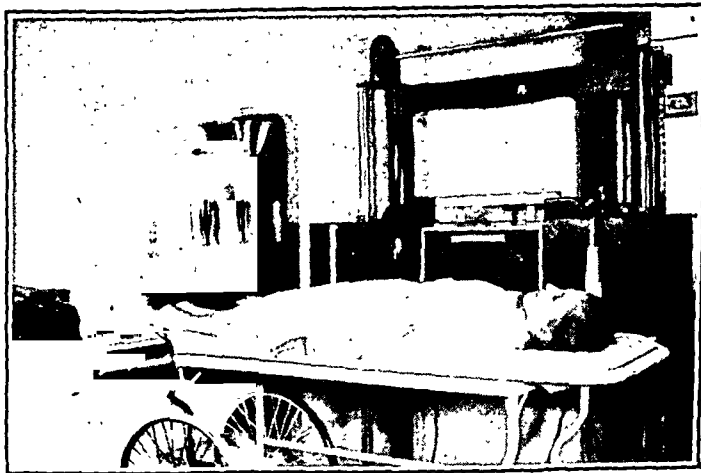


FIG. 6.—Position of the patient for demonstrating the presence of intra-abdominal adhesions.

closed off with a clamp or hemostat to prevent loss of the gas; the atomizer bulb is re-attached to outlet "B"; and the apparatus is ready for use.

The abdomen is entered in the midline (linea alba), after preliminary surgical preparation and anesthetizing of the site of puncture, by means of a spinal puncture needle. Following entry into the peritoneal cavity, the stilet is withdrawn from the needle, and the latter plugged into the Luer adaptor attached to the sterile unit shown in Figure 2.

By means of the atomizer bulb a layer of compressed air is produced above the water in the distal bottle, which forces this liquid medium over into the proximal bottle. As the water rises up in the latter receptacle, it pushes the CO₂ lying above, out through the sterile unit and into the patient's abdominal cavity. Somewhere between 1500 and 3000 cc. is introduced. Patients who have had considerable ascitic fluid require and tolerate a larger quantity of gas than those who have not had ascites. Obviously this transudate should be largely removed before inducing artificial pneumoperitoneum.

Roentgenograms are taken at 2 meters, for which an upright Bucky diaphragm is useful but not necessary, as we have gotten excellent pictures without its use. The

spleen is best visualized by having the patient lie with his right side down, and facing the Roentgen ray plate (Fig. 3). The reverse is used to outline the liver (Fig. 4). The sub-diaphragmatic spaces are visualized by exposing the film with the patient standing erect (Fig. 5). This latter position is also used to determine intraperitoneal rupture of the bladder after having injected the carbon dioxide into the bladder *via* the urethra, rather than through the linea alba. Here the quantity injected is much less—only enough to produce a visible gas shadow beneath the diaphragm. Intra-abdominal adhesions to the belly wall are best shown with an exposure made with the patient lying on his back on the table or stretcher (Fig. 6).

By means of this procedure, malignant and/or other lesions high up in the fundus of the stomach, have also been demonstrated which were not seen at routine fluoroscopy. Artificial pneumoperitoneum is induced after having produced a contrast medium within the stomach (either a thin barium suspension or gas generated by administering a Seidlitz powder will suffice). This places a contrast medium on both the inside and outside walls of the stomach, thereby showing both the contour and thickness of same.

REFERENCES

1. LEWIS, B. O.: Artificial Pneumo-peritoneum, *Texas State J. Med.*, **35**, 1, 1939.
2. MOORE, R. M., and BRASELTON, C. W., JR.: Experiments in Gas Embolism, *Bull. Sealy Hosp. and Univ. of Texas School Med.*, **1**, 78, 1939.

THE OCCURRENCE OF FIBRINOLYSIS IN SHOCK, WITH OBSERVATIONS ON THE PROTHROMBIN TIME AND THE PLASMA FIBRINOGEN DURING HEMORRHAGIC SHOCK*†

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THERE are reports in the medical literature about a peculiar phenomenon affecting the blood clot called fibrinolysis. It may be described as follows: if blood is taken in a test tube without an anticoagulant and allowed to clot, it is sometimes observed that the clot disappears completely in the following minutes or hours. The blood becomes fluid again and cannot be clotted by the addition of thrombin, because the blood no longer contains fibrinogen. Fibrinolysis as defined in this paper has never been observed in the blood of normal subjects in this clinic. It has been reported to occur after the intravenous injection of peptone in dogs.⁷ After callicrein injections into dogs, striking changes in the clotting of blood have been observed, which may be due to fibrinolysis.¹⁷ In humans, it is sometimes observed following intravenous injection of typhoid vaccine⁵ and is frequently seen in the rare fatal shock following intravenous injection of mercurial diuretics.¹⁸ In a recent communication, Van S. Smith described the occurrence of fibrinolysis in the blood of patients during toxemia of pregnancy.¹¹

In humans, the most extensive investigation on fibrinolysis was carried out in Russia during the development of the technique of preparing cadaver blood for transfusion.¹⁹ It was noted by Yudin and his associates¹⁹ that the blood of patients following sudden death underwent very rapid fibrinolysis, while that of patients dying as a result of a chronic disease showed no evidence of lysis of the clot. It was also observed that the blood of patients dying suddenly was often uncoagulable and that this was due to the absence of fibrinogen in the blood. Therefore it was found possible to store cadaver blood obtained from patients dying suddenly for transfusion purposes without the addition of an anticoagulant.

While these observations on dogs and humans are well known and generally accepted, no attempt has been made to determine the common factor, if any, which may be present in all of these conditions in which fibrinolysis occurs. From a study of the circumstances presented in the literature it seems possible that at least one of the common factors might be

* The work described in this paper was done in part under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

† This study was aided in part by a grant "In recognition of Dr. Francis W. Peabody's services to the Foundation" from the Ella Sachs Plotz Foundation.

the existence of peripheral vascular failure in the patients in which fibrinolysis was found. It is known that peripheral vascular failure occurs in peptone and typhoid vaccine shock as well as in that following the intravenous injection of mercurial diuretics. The cases studied by Yudin and his associates¹⁹ were, in general, patients dying of hemorrhagic or traumatic conditions, or else from acute, non-infectious medical illnesses in which peripheral vascular failure was a part of the clinical picture.

The present communication presents evidence concerning the occurrence of fibrinolysis in the blood of patients suffering from shock due to different causes, and in dogs with hemorrhagic shock.

Observations on Humans. *Methods.* For the purpose of this study, fibrinolysis is defined as a complete dissolution of the fibrin clot produced by coagulation of whole blood or plasma in the time interval of a few hours. Reduction in the size of the clot was excluded as a criterion because of the difficulty in distinguishing between true fibrinolysis and clot retraction. Fibrinolysis occurring after 24 hours was excluded because of the possibility of bacterial contamination of the sample. The amount of fibrinolytic activity present could be roughly estimated by the speed with which complete dissolution took place.

Two methods were used in the detection of fibrinolysis. The first method consisted of taking a sample of venous or arterial blood without an anticoagulant and permitting it to coagulate in a chemically clean glass test tube, observing the time of the disappearance of the clot at 37° C. if this phenomenon occurred. The second method consisted of taking venous or arterial blood and mixing it with either sodium citrate or a mixture of potassium ammonium oxalates as an anticoagulant. The final concentration of citrate in the sample was 0.25% and that of oxalate was 0.2%. Plasma was obtained from the blood by centrifuging at 1500 to 2000 r.p.m. for 15 minutes. 0.1 ml. of the plasma was transferred to a chemically clean glass tube, diluted with 0.2 ml. of saline and recalcified with 0.1 ml. of 0.25% calcium chloride. Alternatively, clotting was produced by the addition of 0.1 ml. of a 1.25% thrombin solu-

tion. The clots so formed were observed for fibrinolysis at 37° C. The thrombin solution used was Lederle "Clotting Globulin." This material has been repeatedly shown to be devoid of fibrinolytic properties.¹⁴ The patients studied here were admitted to the Boston City Hospital except one who was observed in another clinic. They were suffering from a variety of conditions. The usual clinical criteria for the presence of peripheral vascular failure were used, namely, rapid thready pulse, low blood pressure, cold and clammy extremities. In all, 22 patients were studied.

Results. The results of the studies on human subjects are shown in Table 1. It will be observed that of the 22 patients studied, fibrinolysis occurred in 8 individuals. With one exception, all these patients were in shock at the time fibrinolysis was observed. Three of the cases of shock were associated with extensive thermal burns and 4 with hemorrhage. The patient whose blood showed fibrinolysis and who was not in shock was admitted in coma probably induced by a fatal dose of some barbiturate. At the time that fibrinolysis was observed in his blood, he exhibited respiratory difficulties of a serious nature consisting of slow respirations alternating with periods of complete apnea, and he was deeply cyanosed.

In 3 patients with thermal burns the observations on fibrinolysis were repeated over a considerable period of time and it was noted that the fibrinolysis which had been present during the period of shock disappeared after shock had been effectively treated.

Case Reports. All observations were carried out on venous blood except in the case of the patient L. J., in whom arterial blood was studied.

I. Burns. L. J. (B.C.H. 1166403), a 6 year old girl, had a flame burn over 65% of body surface, chiefly 3rd degree. Admitted in profound shock. Fibrinolysis present in diluted plasma on admission (time of dissolution 3 to 18 hours). No observation made on whole blood. Fibrinolysis absent after period of shock. Surface treatment:

triple dye. Treatment of shock: serum, blood and electrolyte solution. Temperature never exceeded 100°. Died suddenly on the 3rd day after admission, in coma and convulsions.

M. F. (B.C.H. 1163418), a 78 year old male, had a flame burn over 35% of body surface, mixed 2nd and 3rd degree. Admitted in profound shock. Fibrinolysis present on admission in diluted plasma (time of dissolution 25 minutes). No observation made on whole blood. Fibrinolysis absent after period of shock. Surface treatment: triple dye. Shock treated with plasma, blood and electrolytes. Died 18 hours after admission.

on recalcification or addition of thrombin. The clot redissolved completely in 24 hours. The patient died before any attempt to treat her could be made.

G. W. (B.C.H. 1161340), a 59 year old male with portal cirrhosis, was admitted in severe shock due to bleeding esophageal varices. Treated unsuccessfully with transfusions of plasma and blood. Died shortly thereafter. Fibrinolysis observed in whole blood (rate of dissolution less than 12 hours) and in diluted plasma clotted by thrombin (rate of dissolution 25 minutes).

III. *Medical Illnesses.* M. L. (B.C.H. 1168315), a 32 year old male, was admitted in coma (probable barbiturate poisoning).

TABLE 1.—FIBRINOLYSIS IN SHOCK (IN MAN)

	No. of cases	Fibrinolysis
Burns:		
Shock	3	3
No shock	3	0
Hemorrhagic shock	4	4
Traumatic injury:		
Shock	1	0
No shock	4	0
"Medical" shock	7	1

H. H. (B.C.H. 1160599), a 74 year old male, had a flame burn over 75% of body surface, chiefly 3rd degree. Admitted in shock. Fibrinolysis in diluted plasma present on admission; time of dissolution 3 hours. No observation made on whole blood. Fibrinolysis absent after period of shock. Surface treatment: triple dye. Treatment of shock: plasma and electrolyte solution. Patient died 17 hours after admission.

II. *Hemorrhagic Shock.* C. H. (case contributed by Dr. G. K. Mallory), a 32 year old female, had severe postpartum hemorrhage treated with transfusion of blood and finally hysterectomy. Patient died shortly thereafter. Whole blood taken shortly before death never clotted. After spinning, the supernatant (0.1 cc.) added to fibrinogen solution (0.1 cc.) produced a clot which redissolved in 1 hour.

G. P. (B.C.H. 1131225), a 62 year old male with portal cirrhosis, was admitted in severe shock due to intractable epistaxis and hematemesis. Whole blood clotted and redissolved in 12 hours. The patient survived.

S. A. (B.C.H. 1142691), a 38 year old female, was admitted in severe shock due to massive rectal hemorrhage (etiology unknown). Diluted citrated plasma clotted

Patient died 9 hours after admission. He was never in shock. Respiration was labored and interrupted by long periods of apnea. Fibrinolysis observed in diluted plasma clotted with thrombin and with calcium (rate of dissolution 1 hour) obtained from blood taken 2 hours after admission. At that time the patient was apneic. Two subsequent samples did not show fibrinolysis.

Of the 14 patients who showed no fibrinolysis, 3 were suffering from injuries due to thermal burns but were not in shock at the time when the blood samples were taken and were never in shock during their course in the hospital. Five patients had had severe traumatic injuries but in only one instance was shock present at the time of study; the state of shock was moderately severe. Six other patients were seriously ill from acute medical disorders and were all in a state of peripheral vascular failure at the time of their study.

Experimental Observations on Dogs
Methods. Nineteen (not selected) mongrel dogs, weighing between 6 and 14 kg., were used as experimental animals. Two different types of experiments were performed.

In the first type, 13 dogs (Nos. 1 to 13) were used. Eleven of them were anesthetized by the intravenous or intraperitoneal injection of 30 mg. of nembutal per kg. of body weight before the observations were made. Two animals (Nos. 6 and 13) were studied without general anesthesia; these 2 dogs received 5 mg. of morphine per kg. subcutaneously immediately before the experiment and local anesthesia with procaine at the site of the operative procedure. The blood pressure was recorded by a mercury manometer and kymograph. A No. 14 hypodermic needle was inserted in the femoral artery and the recording system was filled with saline. No anticoagulant was used. The needle was kept patent by washing it out every 5 or 10 minutes with small quantities of isotonic salt solution. Hypotension was produced by one large bleeding and maintained at the desired level by repeated small bleedings from the femoral artery. An attempt was made to maintain the blood pressure below 40 to 50 mm. of mercury; there were often fluctuations of the blood pressure since the deliberate avoidance of an anticoagulant precluded the use of automatic devices described by several authors. During the period of shock, the animal's blood pressure was so delicately balanced that it was necessary to reinject small quantities of saline or occasionally citrated blood following the removal of the necessary samples for observation. The blood samples were obtained from the femoral artery and in certain instances from the jugular vein.

In the second type of experiments, carried out on 5 dogs (Nos. 13 to 18), no general anesthesia and no morphine were used; local anesthesia by procaine or novocaine was used at the site of the operative procedure. A paraffined glass cannula was inserted in the femoral artery or deep into the jugular vein and blood was allowed to flow freely until death of the animal. This occurred between 5 and 18 minutes after the beginning of the bleeding. The blood pressure was not measured. Blood samples were obtained every 1 or 2 minutes from the flow through the paraffined cannula.

In the two series of experiments, the blood samples were taken simultaneously with and without anticoagulant. Sodium citrate in a final concentration of 0.25% was added as an anticoagulant and the plasma was removed as rapidly as possible by centrifuging.

It was then either studied immediately or frozen at -30°C . and kept at that temperature. The frozen samples were thawed at 37°C . at the time of study.

The method of observing fibrinolysis and the criteria of evaluation were those described in the human investigations. In addition to the study of fibrinolysis, prothrombin time by the method of Quick⁹ and fibrinogen determination by the method of Cullen and Van Slyke² were carried out in a certain number of instances. In all cases in which the prothrombin time was found prolonged, the measurement was repeated after addition of fibrinogen to the sample, in order to rule out an artificially prolonged prothrombin time due to deficiency of fibrinogen in the plasma sample. To rule out the possibility of the presence of an anticoagulant in the samples showing a prolonged prothrombin time, they were tested for anticoagulant as described previously.¹³

I. Sustained Shock. Results. The data are given in Table 2. Fibrinolysis was observed during the shock period in 5 of 13 experiments (Dogs 1, 3, 6, 7, 13). In no instance did fibrinolysis occur during the first 2 hours following the onset of shock. In Dog 3, simultaneous samples of venous and arterial blood were obtained from the femoral artery and the jugular vein. Fibrinolysis occurred first in the venous sample and subsequently in both the venous and arterial samples (Fig. 1). No fibrinolysis was observed in the blood of 8 animals (Dogs 2, 4, 5, 8, 9, 10, 11, 12). In these animals the duration of shock did not exceed 3 hours, with the exception of Dog 9 in which no fibrinolysis was seen, although the period of shock was 6 hours. In most instances the clot was well formed except in the samples of blood obtained from Dogs 1 and 3. In these animals at the time when fibrinolysis was present the formation of the clot was poor and after dissolution additional small fibrin clots occurred followed by resolution. The resolution of these small clots was complete in a few minutes and their presence could have been easily missed. Had this occurred the results might have been falsely interpreted as an absence of coagulation.

In no instance was fibrinolysis observed in the blood samples taken before the induction of shock or in any blood sample obtained during the first 2 hours after acute hemorrhage. The earliest appearance of fibrinolysis was 2½ hours (Dog 6), and the latest 5 hours (Dog. 13). Once fibrinolysis had appeared it persisted in all subsequent samples until the death of the animals. Since all the animals died it was impossible to make observations on

the fibrinolytic properties of the blood following recovery from hemorrhagic shock.

On 8 dogs, determinations of the prothrombin time were made simultaneously with the observations on fibrinolysis. The results are given in Table 3. The data show that the prothrombin time became somewhat more prolonged as the condition of shock persisted. The addition of fibrinogen to the plasma did not correct

TABLE 2.—FIBRINOLYSIS IN HEMORRHAGIC SHOCK (DOGS)

Occurrence of Fibrinolysis								
Dog No.	Control	Hour after beginning of shock						Rate of fibrinolysis
		1	2	3	4	5	6	
1	0	0	0	0	+	Died	..	30 min.
2	0	0	Died					
3	0	0	0	+	Died	30 min.
4	0	0	0	Died				
5	0	0	Died					
6*	0	0	+	+	Died	60 min.
7	0	0	0	+	+	Died	..	15 hrs.
8	0	0	Died					
9	0	0	0	0	0	0	0	
10	0	0	0	Died				
11	0	0	0	0	Died			
12	0	0	0	0	Died			
13*	0	0	0	0	0	+	Died	1 hr.

* No anesthesia.

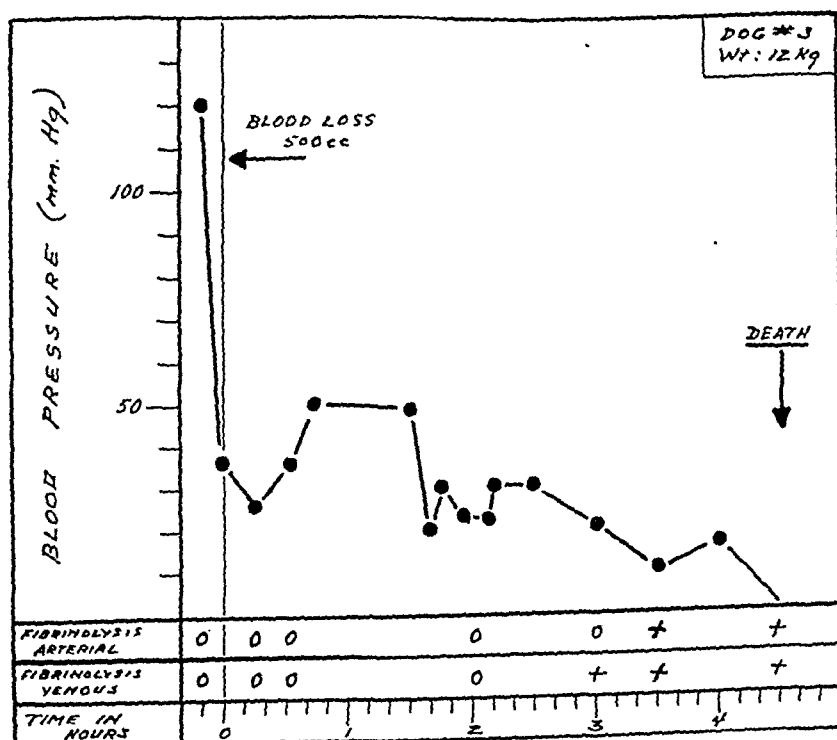


FIG. 1.—Comparison of fibrinolytic activity in venous and arterial blood in hemorrhagic shock in dog.

the prolongation of the prothrombin time, indicating that it was not due to a lack of fibrinogen in the samples of plasma. The failure of the plasma obtained during the shock phase to prolong the clotting time of normal dog or human blood was taken as an indication that there was no circulating anticoagulant produced during the shock phase.

II. Rapidly Fatal Bleeding. The data are given in Table 5. Fibrinolysis was observed in 3 instances in the last sample of blood obtained while there was still a flow of blood through the cannula (Dogs 14, 15, 17). At this time the dog was dying.

Prothrombin time and fibrinogen determinations on the samples of blood in this

TABLE 3.—PROTHROMBIN IN HEMORRHAGIC SHOCK (DOGS)

Dog No.	Control	Quick Prothrombin Time (Seconds)					
		Hour after beginning of shock					
		1	2	3	4	5	6
6*	13	14	17	20	Died		
7	11	12	19	24	32	Died	
8	11	12	Died				
9	11	11	12	13	17
10	12	15	19	Died			
11	12	14	17	19	23	Died	
12	13	20	26	Died	
13*	11	11	13	15	18	21	Died

* No anesthesia.

TABLE 4.—FIBRINOGEN IN HEMORRHAGIC SHOCK (DOGS)

Dog No.	Control	Fibrinogen (Mg. per 100 cc. Plasma)					
		Hour after beginning of shock					
		1	2	3	4	5	6
9	256	102
10	294	144	Died				
11	592	244	226	209	Died		
12	732	245	263	Died	
13*	346	..	150	..	132	116	

* No anesthesia.

TABLE 5.—FIBRINOLYSIS DURING RAPIDLY FATAL BLEEDING

Dog No.	Control	Occurrence of Fibrinolysis													Rate of fibrin- olysis
		Time from beginning of bleeding													
		2	4	6	8	10	12	14	16	18	20	30	40	60	
14	0	0	..	0	+	Died	24 hrs.
15	0	0	0	+	Died	3 hrs.
16	0	0	0	0	Died	
17	0	0	0	+	Died	3 hrs.
18	0	..	0	..	0	..	0	..	0	Died	
19	0	..	0	0	0	0	Died	

On Dogs 9, 10, 11, 12, 13, determinations of the fibrinogen level in the plasma were carried out simultaneously with prothrombin determinations and observation on fibrinolysin. In all 5 there was a marked and progressive fall of the fibrinogen, paralleling roughly the fall in prothrombin. In all cases, the fall in these constituents preceded the appearance of detectable fibrinolysis (Table 4).

type of experiment showed no significant change from the control values.

Discussion. Observations in this laboratory on many hundreds of samples of blood on normal individuals have shown that fibrinolysis never occurs in whole blood or plasma clotted by recalcification or on the addition of thrombin, within an observation period of 24 hours. Therefore, it would appear that the fibrinolysis re-

ported here cannot be accounted for on the basis of bacterial contamination or other artifacts, since in no instance was an observation made for longer than 24 hours and the actual time required for the complete digestion of the clot was much shorter than this time interval.

The present observations in humans strongly suggest some interrelation between the presence of peripheral vascular failure due to burn or hemorrhage and the presence of fibrinolysis. All the patients whose blood showed fibrinolytic activity were in shock, and, in two of them, the fibrinolysis disappeared on recovering from the peripheral vascular collapse. In contrast, none of the six patients with serious medical illnesses, who were in peripheral vascular failure, showed fibrinolysis. The 1 patient who was not in shock showed definite evidence of marked anoxia due to anoxemia. Since it is highly probable that peripheral vascular failure is associated with anoxia, it is possible that the precipitating cause of the existence of fibrinolysis is the existence of a prolonged anoxic state. It would appear that, in the small group of patients studied here, fibrinolysis was most frequently associated with shock produced by hemorrhage and burns, and, less frequently, with peripheral vascular collapse associated with medical illnesses. Further observations are needed before this point can be clearly demonstrated.

Generally speaking the experimental evidence obtained on dogs in hemorrhagic shock as reported here is in agreement with the results of the observations on the patients in hemorrhagic shock. In the first series of experiments, the occurrence of fibrinolysis was observed in 5 dogs, 2 of which were not anesthetized (Nos. 6 and 13). However, in these 5 animals, fibrinolysis was never observed earlier than 2 hours after the onset of shock. All but 1 (No. 9) of the 8 dogs in which fibrinolysis was not observed died before the 4th hour after the onset of shock, 3 of them (Nos. 2, 5, 8) dying quite early, and it is conceivable that the rapid death

may explain the absence of fibrinolysis. It should be pointed out that by the method used in this work, complete disappearance of the clot is taken as evidence of fibrinolysis. It is entirely possible that fibrinolysis may be present before it becomes intense enough to bring about complete dissolution of the clot and that more sensitive methods of detection would demonstrate its occurrence before complete dissolution occurs. However, the present data would indicate that fibrinolysis is produced by the presence of the shock state rather than preceding it.

In the second series of experiments, fibrinolysis was observed in 3 of 5 dogs and, in all cases, it appeared only in the last sample of blood, obtained shortly before death. In this series of experiments, the time of appearance of fibrinolysis, counted from the beginning of the bleeding, was quite in contrast with that seen in the first series. The difference in the time relationship may be due to the more rapid and abrupt type of disturbance produced in the second series of experiments as compared to the first ones. The second type of experiments was performed precisely in order to bring out this point.

From the data reported here the prolongation of the prothrombin time observed in 8 experiments on dogs seemed to be a constant occurrence when the state of shock produced by hemorrhage was of sufficient duration and intensity. It cannot be explained by the presence of an anticoagulant. Also it was not due to a deficiency of fibrinogen in the plasma since it was not corrected by the addition of fibrinogen to the plasma. It seems therefore that the prolongation of the prothrombin time in these experiments was actually due to hypoprothrombinemia. As far as we know, this is the first time that the occurrence of hypoprothrombinemia has been reported in hemorrhagic shock. Theoretically, hypoprothrombinemia can be explained on the basis of vitamin K deficiency, liver dysfunction, intravascular coagulation or destruction of the prothrombin by enzymatic digestion. No data

are available to indicate the possible influence of hemodilution, which occurs in hemorrhagic shock, in bringing down the prothrombin concentration in the blood of the dogs studied here, but it does not seem probable that hemodilution alone could explain changes in the prothrombin as marked as reported here. Vitamin K deficiency usually does not manifest itself in a period of a few hours although it is conceivable that it might do so during shock, in which state an increased demand for other vitamins has been observed.²⁰ Liver dysfunction is a conspicuous manifestation of hemorrhagic and traumatic shock and liver dysfunction could constitute the cause of the hypoprothrombinemia reported here.^{1,16} Final proof that such is the case would seem difficult to obtain in view of the fact that hepatectomy is by itself a very serious operative procedure which may produce shock and since hemorrhagic shock alone is able to produce hypoprothrombinemia, it would seem that no conclusion can be reached from a comparison of the rates of disappearance of prothrombin in hepatectomized and shocked animals.

The intravenous injection of certain proteolytic enzymes is known to cause a reduction of the prothrombin level, either by promoting intravascular coagulation with the consumption of the plasma prothrombin¹³ or by their direct action of digesting prothrombin *in vivo*.¹⁵ In both cases, the reduction in prothrombin is paralleled by a decrease of the fibrinogen level of the plasma. Fibrinogen determinations on 5 dogs carried out in 5 experiments reported here showed a significant reduction in the level of fibrinogen concomitant with the fall in prothrombin. There is therefore a possibility that the hypoprothrombinemia and fibrinogenopenia in hemorrhagic shock might be due to the fibrinolytic activity. The data obtained so far do not offer any evidence as to whether the decrease in prothrombin and fibrinogen is due to such a direct digestive action or due to a slow intravascular coagulation.

It would seem that the hypoprothrombinemia and fibrinogenopenia observed in hemorrhagic shock, as reported here, may be of importance in the evaluation of the therapy of shock in humans. It may indicate that the usefulness and indications of blood and plasma substitutes devoid of prothrombin and fibrinogen should be reconsidered if shock in humans results in similar reduction in prothrombin and fibrinogen. If such were the case, it is probable that any fluid used in the treatment of shock, in addition to fulfilling the well known requirements, should be able to replace the deficient constituents. In that respect, whole blood and those preparations of plasma, containing normal amounts of prothrombin and fibrinogen, have no adequate substitutes.

The absence of fibrinolysis in certain cases of peripheral vascular failure in humans can be explained either by the absolute absence of fibrinolysis or, equally well, by a failure on our part to obtain a blood sample at the time when fibrinolysis was present. At present nothing is known about the exact conditions and the time relations under which fibrinolysis appears following human peripheral vascular failure. From the experimental data it would appear that fibrinolysis as determined by the present method is not observable at all times during the shock state. Furthermore, the transient nature of the phenomenon is obvious for it completely disappears when the shock present is adequately treated. The transient nature of the phenomenon could well explain our failure to observe it in all cases of shock. It is possible that a more sensitive method than the one used here would be able to detect fibrinolysis in a greater number of cases.

Final proof is not available to demonstrate that the phenomenon of fibrinolysis is due to proteolysis. However, it has been previously demonstrated that fibrinolysis can be produced by artificial means in normal plasma, as for example, by shaking the plasma with chloroform. Under these circumstances the fibrinolytic activity is accompanied by or associated with the

production of proteolytic enzyme.¹⁴ Recently, it has been shown that fibrinolysis produced by streptococcus toxin is probably enzymatic in nature.⁶ Therefore, reasoning by analogy it is probable that the fibrinolysis reported in this communication may likewise be due to proteolysis.

One may speculate on an origin of the fibrinolytic enzyme. It could originate from the plasma itself due to an activation of an inactive precursor of a plasma enzyme,¹² or it could arise from cellular elements of damaged tissue. Present evidence does not permit a definite conclusion on this point. The latter probability is suggested by the fact that in one experiment the fibrinolytic activity was found to be present in venous blood a long time before it appeared in arterial blood. This observation could be interpreted as meaning that there was a release of intracellular elements in the blood stream.

It has been demonstrated^{10,13,15} that certain proteolytic enzymes are toxic when injected intravenously. In fact they are able to produce a state of shock in experimental animals. This type of shock is associated with changes in the blood

coagulation mechanism, some of which are not unlike those, reported here, following hemorrhagic shock in dogs. Therefore, if fibrinolysis is caused by a proteolytic enzyme, it is probable that the presence of such an enzyme in the blood stream during shock might well constitute a sustaining and aggravating factor. Its relation to shock as an initiating factor is not at present clear.

Summary. 1. The spontaneous dissolution of a whole blood clot or one of diluted plasma is called fibrinolysis. The occurrence of fibrinolysis was observed in 8 out of 22 severely ill patients.

2. Of the 8 patients whose blood showed fibrinolysis, 4 were in severe hemorrhagic shock, 3 in severe shock due to extensive flame burns, 1 was poisoned probably by some barbiturate.

3. In hemorrhagic shock produced experimentally in 13 dogs, fibrinolysis was observed in 5 instances. In 6 dogs with rapid fatal bleeding fibrinolysis occurred three times.

4. In hemorrhagic shock in dogs, there was a marked and progressive fall in the levels of prothrombin and fibrinogen in the plasma.

REFERENCES

1. ANDRUS, W. DEW., LORD, J. W., JR., and MOORE, R. A.: *Surgery*, 6, 899, 1939.
2. CULLEN, G. E., and VAN SLYKE, D. D.: *J. Biol. Chem.*, 41, 587, 1920.
3. EBERT, R. V., STEAD, E. A., JR., and GIBSON, J. G., 2d: *Arch. Int. Med.*, 68, 578, 1941.
4. ENGEL, F. L., HARRISON, H. C., and LONG, C. N. H.: *J. Exp. Med.*, 79, 9, 1944.
5. HAM, T. H.: Personal communication.
6. KAPLAN, M. H.: *Proc. Soc. Exp. Biol. and Med.*, 57, 40, 1944.
7. NOLF, P.: *Arch. Int. Physiol.*, 3, 1, 1905.
8. QUICK, A. J.: *The Hemorrhagic Diseases*, Springfield, CHARLES C Thomas, Chap. XII, 1942.
9. QUICK, A. J., STANLEY-BROWN, M., and BANCROFT, F.: *AM. J. MED. SCI.*, 190, 501, 1935.
10. ROCHA E SILVA, M.: *Arch. Path.*, 33, 387, 1942.
11. SMITH, V. S.: Seminar Conference, Department of Physical Chemistry, Harvard Medical School, 1945.
12. TAGNON, H. J.: *J. Lab. and Clin. Med.*, 27, 1119, 1942.
13. TAGNON, H. J.: *J. Clin. Invest.*, 24, 1, 1945.
14. TAGNON, H. J., DAVIDSON, C. S., and TAYLOR, F. H. L.: *J. Clin. Invest.*, 21, 525, 1942.
15. TAGNON, H. J., WEINGLASS, A. R., and GOODPASTER, W. E.: *Am. J. Physiol.*, 143, 644, 1945.
16. WARNER, E. O.: *J. Exp. Med.*, 68, 831, 1938.
17. WESTERFELD, W. W., WEISIGER, J. R., FERRIS, B. G., JR., and HASTINGS, A. B.: *Am. J. Physiol.*, 142, 519, 1944.
18. WEXLER, J., and ELLIS, L. B.: *Am. Heart J.*, 27, 86, 1944.
19. YUDIN, S. S.: *Lancet*, 2, 360, 1937.
20. Unpublished observations from this laboratory.

OBSERVATIONS ON THE SPECIFICITY AND CLINICAL USE OF DIROFILARIA
IMMITIS ANTIGEN IN THE DIAGNOSIS OF HUMAN FILARIASIS
(WUCHERERIA BANCROFTI)

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THE incidence of filariasis among American troops located in endemic areas in the South Pacific has increased the importance of this disease, and has brought new problems to the attention of the medical department. Outstanding is the need for further laboratory aids in the diagnosis of early human filariasis. The findings of lymphangitis, lymphadenopathy, epididymo-funiculitis, orchitis, and scrotal swelling, associated with service in known filarial endemic areas may be regarded as good clinical evidence for filariasis. Nevertheless, it is necessary to rule out other etiologic agents for the above signs and symptoms and to have laboratory confirmation of the disease.

It has been pointed out by King⁶ that a positive diagnosis for filariasis may be made by three methods: microscopic demonstration of adult filaria in biopsy specimens, demonstration of microfilariae in the blood stream, and the demonstration of calcified worms by Roentgen ray technique.¹² These methods depend on the finding of either the larval or adult worm in the human host. Thus far only the biopsy procedures^{10,14,15,17} have been reported successful. Although microfilariae have been found in abundance in the peripheral blood of infected natives, the blood stream of American soldiers has been reported persistently negative to the present time. Roentgen ray examinations have not been of diagnostic value.

Although positive evidence from biopsy examination is definite and incontrovertible, this procedure contains certain disadvantages for routine usage. It is time consuming, requires surgical intervention, and furthermore a negative biopsy may

require removal of an additional gland for further study. Finally, the biopsy procedure is not applicable to an investigation of filariasis in a group survey. Consequently, it was decided to study the possibility of using a test involving an increased sensitivity of the individual. Experimental work has already been reported on the intradermal response and serologic tests with an antigen prepared from the dog heart worm, *Dirofilaria immitis*.

In 1930, Taliaferro and Hoffman¹⁶ reported the use of a 1:200 dilution of a saline extract of *Dirofilaria immitis* antigen in cutaneous tests. Fairley^{4,5} used a dilution of 1:200 and 1:1000 of a saline extract of *Dirofilaria immitis* for both intradermal and complement fixation tests. He injected 0.25 cc. and obtained positive reactions in many suspected cases. Further work on the complement fixation reaction with the *Dirofilaria* antigen was carried out by Lloyd and Chandra.⁸ In a series of 89 cases showing clinical symptoms of filariasis, 26% gave a positive response. In a series of 15 cases with helminthic infections other than *Wuchereria bancrofti*, 3 positive results were obtained. In all 3 cases, the parasitic worm was *Dracunculus medinensis*.

In the more recent studies, Dickson, Huntington and Eichold³ investigated the intradermal response of Navy personnel stationed on Samoa. Using an extract of *Dirofilaria immitis* and working with two groups, the authors obtained a positive reaction in 83.1% of a group of 137 patients showing clinical filariasis. In a second control group of 128 individuals who showed no symptoms and had been

4 weeks or less in the endemic area, a positive reaction was obtained in 4.7%. These authors further state that in one instance an adult filarial worm was found in a patient with a negative skin test, indicating that desensitization may have taken place. Comparative tests with an extract of *Ascaris lumbricoides* revealed a certain degree of cross-reactivity. Since the authors give no information concerning the dosage and dilution, it is difficult to draw any conclusions.

In 1944, Michael¹⁰ reported the results of skin tests with *Dirofilaria* antigen on 307 patients with filariasis. He obtained a positive response in 87.3%. King⁶ using a 1:1000 dilution of *Dirofilaria* antigen obtained a positive response in 90.8%.

In an attempt to arrive at a dilution of the *Dirofilaria* antigen which would be specific for filariasis, Bozicevich and Hutter¹ injected 0.01 cc. intradermally using a number of dilutions. They obtained positive results in 25 patients with a dilution of 1:8000, and were able to conclude that this dilution would screen out false positive reactions due to allergies and malaria. Complement fixation studies were negative.

The possibility of using the microfilaria of *Wuchereria bancrofti* in preparation of an antigen was investigated by Oliver-Gonzalez and Berceowitz.¹³ These authors carried out precipitin tests and obtained 2 positive reactions from 26 patients with microfilariae in the blood and 3 positive reactions from 14 patients with clinical filariasis.

Additional work has been reported on the use of an extract prepared from *Litomosoides carini* (Culbertson, Rose and Demarest).² Thus far there is no evidence that this extract is superior to one prepared from *Dirofilaria immitis*.

In view of the lack of sufficient data on the problem of cross-reactions in patients with intestinal helminths and on the specificity of this antigen, it was thought worth while to investigate these problems. We have attempted, by a titration of the *Dirofilaria* antigen, to determine first, the

dilution at which false positives due to intestinal helminths may be ruled out and, second, the sensitivity of patients with filariasis to the antigen. In addition it was possible for us to compare results obtained from both biopsies of lymph nodes and skin tests on the same patients.

Material and Methods. In the early stages of this investigation, the antigen was prepared according to the method of Huntington as reported by Michael.¹¹ Certain minor modifications were made during the investigation and the procedure was standardized in the following manner. Dogs were sacrificed by an intravenous injection of magnesium sulfate and their hearts removed. An incision was made immediately into the right ventricle and auricle and the adult *Dirofilaria immitis* worms were removed and placed in an evaporating dish containing physiologic saline. They were carefully cleaned of any clotted blood and placed in running water overnight. On the following morning the worms were washed in several changes of distilled water and then treated with three changes of acetone, following which they were placed in an incubator (37° C.) to dry. After 12 hrs., the worms were thoroughly dried. They were then ground up in a mortar and pestle, and the powder kept, well corked, in a refrigerator.

The extract was prepared by weighing out the powder and making a 1% suspension in physiologic saline. The extraction was allowed to proceed for 2 hrs. at 37° C. with constant stirring. The extract was then sterilized by filtration through a Seitz filter and phenol added to make a 0.3% concentration. From this stock extract (1:100) the following series of dilutions were made for use in the titration of the antigen: 1:200, 1:2000, 1:4000, 1:8000 and 1:16,000.

It has been an observation of this laboratory that the extracted material will lose its potency. Consequently the dried powder was kept as the stock source and new dilutions were made every month. The lack of knowledge as to the chemical nature of the antigenic substance made it necessary to check the potency of the extract very carefully. In an attempt to refilter a contaminated batch of the extract, a decided loss in potency was noted. This observation

has since been reported by King⁶ who went on to postulate that we may not be dealing with a true solution and "that perhaps part of the antigenic fraction is held in suspension in the saline solution."

In drying the adult worms after treatment with acetone, it is necessary to watch the temperature. A loss in potency was obtained when the temperature rose above 37° C.

For a control in the intradermal tests, a fragment of dog heart was removed and treated identically as the antigen. This was made up to a dilution of 1:2000 and stored with the antigen in the refrigerator.

In running the skin tests, a volume of 0.05 ml. was injected intradermally on the volar surface of the arm. One arm received an injection of the control material and antigen dilutions of 1:200 and 1:2000. The other arm received the three remaining dilutions of 1:4000, 1:8000, and 1:16,000. At first the reaction was read at 30 min., 1 hr., and 24 hrs. after injection. The 1 hr. reading was soon dropped in favor of a single 30 min. reading, at which time the height of the reaction occurs. In all instances, the 24 hr. reaction was observed and taken into consideration. Occasionally, the arm that received the 1:200 and 1:2000 dilution of *Dirofilaria* antigen revealed an elephantoid reaction at the 24 hr. period.

In determining a positive response, the size of the wheal, diameter of the erythema, and presence of pseudopodia were taken into consideration. A definite increase in wheal size over the control plus an erythema measuring 2 cm. or more was considered positive.

Stools were examined on all patients by the zinc sulfate flotation method and by direct smear. All patients had a minimum of 2 examinations and many had 5 examinations.

Results. The first problem that interested us was to investigate the sensitivity of patients with intestinal helminthiasis to intradermal injections of *Dirofilaria immitis* antigen. A series of 65 patients harboring hookworm, *Strongyloides stercoralis*, *Ascaris lumbricoides*, *Enterobius vermicularis* and *Hymenolepis nana*, all free of clinical filariasis, were injected with the antigen. With one exception, no

positive reaction was obtained with a dilution higher than 1:2000 (Table 1).

The one exception was a patient with herpes zoster in addition to ancylostomiasis. In view of a positive response with the control injection, it was felt that this patient may well be disregarded.

Wright and Murdock¹⁸ obtained cross-reactions with *Dirofilaria immitis* antigen in patients with a dilution of 1:4000. However these authors injected a total volume of 0.1 cc. which is double the volume used in the present study. Consequently the contradiction in results on the cross-reaction is not a real one.

Of 91 patients with clinical symptoms of filariasis injected with the various dilutions of the *Dirofilaria* antigen (Table 2), 83 (91%) gave a positive response to at least one of the dilutions. In a controlled group of 18 individuals with no history of service in an area endemic for filariasis and free of clinical symptoms and signs, 11 gave a negative response to a 1:200 dilution of the antigen, 5 gave a positive response to a 1:200 dilution of the antigen, and 2 gave a positive response to a dilution of 1:2000 of the antigen. No response was obtained at higher titers. Considering the data from the cases with intestinal helminths and from the control cases, it appears that a positive response to a dilution of 1:4000 and higher is indicative of filarial infection. Using this as a basis for the interpretation of our results, we obtained a positive response with the *Dirofilaria* skin test in 78% of the cases.

In an attempt to determine the specificity of the intradermal test with *Dirofilaria* antigen, we were able to compare the results of lymph node biopsy with the results from skin tests (Table 3). In a group of 53 patients, 74% gave a positive skin test to a dilution of 1:4000 to 1:16,000 of the *Dirofilaria* antigen. Biopsies were positive for filariasis in 60% of these cases. It is of interest to note that in several instances more than one biopsy had to be performed on a single patient before a positive gland was obtained. It is possible that further biopsies on the

TABLE 1.—CROSS-REACTIONS OBTAINED WITH DIROFILARIA ANTIGEN SKIN TEST AND HEMATOLOGIC FINDINGS IN 63 PATIENTS WITH INTESTINAL HELMINTHIASIS

Intestinal helminths	No. cases	Dilution giving pos. skin test with <i>Dirofilaria</i> antigen	RBC (mill./c.mm.)	WBC (thous./c.mm.)	Hb. (%)	Lymphocytes (%)	Eosinophils (%)	
							Avg.	Range
Hookworm	11	None	4.4	6.4	91	33	21	7-43
	14	1:200	4.5	9.1	92	34	18	0-31
	12	1:2000	4.5	9.3	96	26	28	2-69
	1	*1:8000	4.7	7.5	92	30	11	
Total	38							
<i>S. stercoralis</i>	5	1:200	4.5	7.2	94	22	14	5-26
	7	1:2000	4.8	8.8	96	30	19	8-23
Total	12							
<i>A. lumbricoides</i>	4	1:200	4.5	9.6	90	29	21	10-29
	2	1:2000	4.7	10.2	92	31	17	12-22
Total	6							
<i>E. vermicularis</i>	2	None	4.2	7.4	88	28	3	2- 4
<i>H. nana</i>	2	None	4.9	6.1	98	36	5	4- 6
	3	1:200	4.6	7.8	95	38	6	4- 8
Total	5							

* The intradermal response to the control solution was also positive. (Patient had herpes zoster in addition to ancylostomiasis.)

TABLE 2.—TITRATION OF THE DIROFILARIA ANTIGEN INJECTED INTRADERMALLY IN PATIENTS WITH CLINICAL FILARIASIS AND THE HEMATOLOGIC FINDINGS

No. cases	Dilution giving pos. skin test with <i>Dirofilaria</i> antigen	Interpretation of skin test	RBC (mill./c.mm.)	WBC (thous./c.mm.)	Hb. (%)	Neutrophils (%)	Lymphocytes (%)	Eosinophils (%)		No. patients showing 6% or more eos.
								Av.	Range	
CLINICAL FILARIASIS										
8	None	Neg.	4.5	9.8	93	64	28	4	0-8	1
10	1:200	Neg.	4.5	8.8	95	56	34	4	1-10	1
2	1:2000	Neg.	4.7	9.7	97	50	43	3	2-4	None
—										
20*										
17	1:4000	Pos.	4.5	8.8	94	59	30	7	2-17	12
25	1:8000	Pos.	4.5	8.8	95	58	30	7	0-29	10
29	1:16000	Pos.	4.5	8.9	93	52	38	8	0-40	7
—										
71†										
CONTROLS—NO CLINICAL FILARIASIS										
11	None	Neg.	4.6	9.0	98	57	35	4	1-7	1
5	1:200	Neg.	4.5	7.8	97	58	35	3	1-5	None
2	1:2000	Neg.	4.8	7.2	99	62	29	4	3-5	None
—										
18										

* Intestinal helminths present in 2 patients.

† Intestinal helminths present in 11 patients.

TABLE 3.—COMPARISON OF RESULTS OBTAINED FROM INTRADERMAL TESTS WITH DIROFILARIA ANTIGEN AND BIOPSY OF LYMPH NODES ON 53 PATIENTS

Test	No.	%
Biopsy—Positive	32	60
Negative	21	40
Skin test*—Positive	39	74
Negative	14	26
Biopsy negative and skin test positive	10	18
Biopsy positive and skin test negative	3	6

* Only reactions to 1:4000 or higher dilutions of the antigen were interpreted as positive.

10 cases with a negative biopsy and positive skin test would bring the two figures into closer agreement.

In 3 cases (6%), a positive biopsy was obtained with a negative skin test. This lack of skin sensitization has also been noted by Dickson, Huntington and Eichold³ and appears to be a true phenomenon and not due to a loss in potency of the extract.

Using the dilutions of 1:4000 and 1:16,000, a survey was made of 55 soldiers at their company aid station. All had been exposed to filariasis, some showing a clinical picture of enlarged nodes, and others clinically free. In this group, 71% gave a positive skin test to the *Dirofilaria* antigen.

Complete blood counts were carried out on all the patients with filariasis (Table 2). No marked deviations from the normal average were noted in the red blood cell count, hemoglobin, neutrophils or lymphocytes. While the average white blood cell count for all the filarial patients was normal, 25% showed an elevation to 10,000 or slightly higher of white blood cells per c.mm.

The eosinophils were elevated in 34% of the entire group of 91 patients showing clinical filariasis. However if we consider only the group with a positive skin test of 1:4000 or greater, 40% showed an elevated eosinophilia. In this latter group, intestinal helminths were found in 15% of the patients.

A diligent search of all cases for microfilaria in the circulating blood failed to give any positive results, even though adult worms containing microfilaria were found by biopsy. All blood was examined by both the fresh smear and by the Knott concentration method.⁷ In the first method a drop of blood was mixed with

a drop of saline and the preparation examined for motile larvæ. In the second procedure, 1 cc. of blood was laked with 10 cc. of 2% formalin. The sediment was smeared out and stained with Giemsa or methylene blue and eosin. Though the variety of *Wuchereria bancrofti* in this area of the South Pacific has a non-periodic larva (Manson-Bahr),⁹ concentrations were made at different intervals of a 24 hour period. In one instance a patient, shown on biopsy to have an adult worm containing microfilariæ in its uterus (Rifkin),¹⁵ have been examined every 2 hours. In several cases, 10 to 20 ml. of blood were removed for concentration, yet negative results were obtained.

Summary. 1. The use of a dilution of 1:4000 of the *Dirofilaria immitis* antigen rules out false positive reactions due to intestinal helminths.

2. In a series of 91 patients with clinical filariasis, 78% gave a positive skin test with a titer of 1:4000 or higher of the *Dirofilaria* antigen.

3. In a group of 53 patients, a positive biopsy was obtained in 60% of the cases and a positive skin test in 74% of the cases.

4. Three patients with a positive biopsy gave negative skin tests.

5. Of a group of 55 soldiers who had been exposed to filariasis (field survey), 71% gave a positive response to a titer of 1:4000 to 1:16,000 of the *Dirofilaria* antigen.

6. An increased eosinophil count was found in 40% of the patients with a positive *Dirofilaria* skin test of 1:4000 or greater.

7. No microfilariæ were found in the peripheral blood though many patients were shown to have adult worms or worm foci in their lymph nodes.

REFERENCES

1. BOZICEVICH, J., and HUTTER, A.M.: Am. J. Trop. Med., 24, 203, 1944.
2. CULBERTSON, J. T., ROSE, H. M., and DEMAREST, C. R.: Am. J. Hyg., 39, 156, 1944.
3. DICKSON, J. G., HUNTINGTON, R. W., and EICHOLD, S.: U. S. Nav. Med. Bull., 41, 1240, 1943.
4. FAIRLEY, N. H.: Trans. Roy. Soc. Trop. Med. and Hyg., 24, 635, 1931.
5. FAIRLEY, N. H.: Trans. Roy. Soc. Trop. Med. and Hyg., 24, 220, 1932.
6. KING, B. G.: Am. J. Trop. Med., 24, 285, 1944.
7. KNOTT, J.: Trans. Roy. Soc. Trop. Med. and Hyg., 33, 191, 1939.

8. LLOYD, R. G., and CHANDRA, S. N.: *Indian J. Med. Res.*, **20**, 1197, 1933.
9. MANSON-BAHR, SIR P. H.: *Trop. Dis. Bull.*, **38**, 361, 1941.
10. MICHAEL, P.: *Naval Med. Bull.*, **42**, 1059, 1944.
11. MICHAEL, P.: Personal communication, 1944.
12. O'CONNOR, F. W.: *Am. J. Roentgenol.*, **23**, 494, 1930.
13. OLIVER-GONZALES, J., and BERCOWITZ, Z. T.: *Am. J. Trop. Med.*, **24**, 315, 1944.
14. PASTERNAK, J.: *Arch. Path.*, **35**, 414, 1943.
15. RIFKIN, H.: *Arch. Path.* (to be published).
16. TALIAFERRO, W. H., and HOFFMAN, W. A.: *J. Prev. Med.*, **4**, 261, 1930.
17. WARTMAN, W. B.: *Am. J. Trop. Med.*, **24**, 299, 1944.
18. WRIGHT, W. H., and MURDOCK, J. R.: *Am. J. Trop. Med.*, **24**, 199, 1944.

THE TREATMENT OF BACILLARY DYSENTERY IN CHINESE SOLDIERS WITH SULFAGUANIDINE AND SULFADIAZINE

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THE opportunity to make controlled observations of the efficacy of sulfaguanidine and sulfadiazine in the treatment of acute bacillary dysentery has recently presented itself to us. In an Army General Hospital in northeastern India caring for Chinese and American troops we have observed many hundreds of cases within the past year. It early became apparent that we were dealing with a relatively benign form of the disease with a uniformly favorable outcome. Under these circumstances it seemed both justifiable and important to utilize the opportunity to determine to what extent sulfonamide therapy shortened the course of the disease or otherwise favorably influenced its course. The present communication describes the results of such an investigation, carried out in the 7 month period from June through December 1943, in which the results of treatment were compared in 334 Chinese patients with bacillary dysentery, one-third of whom received no medication except a placebo, one-third received sulfaguanidine and one-third sulfadiazine.

Method of Study. A tentative diagnosis of bacillary dysentery was made on the history of the sudden onset of abdominal pain, fever and the frequent passage of bloody, mucous stools. On admission to a dysentery ward each patient was immediately placed, without any selection, into 1 of 3 groups, those to receive (a) sulfaguanidine, (b) sulfadiazine and (c) a placebo. After the usual history and physical examination were completed a notation was made as to the duration of the disease prior to admission, and an impression was recorded of whether the patient was slightly, moderately or severely ill. Either on the day of admission or on the following

morning a stool specimen was obtained for gross and microscopic examination and for culture. In making the stool cultures, selected material was emulsified in physiologic saline, and 2 or occasionally 3 surface plates were inoculated. The media employed varied according to availability, and included eosin-methylene blue agar, Leifson's desoxycholate-citrate agar, "Bacto-SS" agar and Endo's agar. At least 2 of these media were used for each specimen. The eosin-methylene blue and the desoxycholate-citrate agar proved most satisfactory. Suspicious colonies were isolated after 18 to 36 hours and identified by cultural characteristics. During the latter half of the study when antisera were available the identity of all strains was confirmed by agglutination against specific antisera, using a microscopic agglutination test with living organisms.

Blood counts were routinely made, and the leukocyte count was repeated every 2nd day if it exceeded 8000 per c.mm. Patients were weighed on admission and on discharge. Medication was begun on the 1st or 2nd hospital day, on the following dosage schedule, either sulfaguanidine, 3.5 gm. every 4 hours, or sulfadiazine in an initial dose of 3 gm., followed by 1 gm. every 4 hours, or a placebo consisting of lactose capsules or colored, flavored water, given 3 times daily. No other drugs were employed. The medication was continued for a variable period of time depending upon the subsequent course of the disease. A strenuous effort was made to insure that each patient drank at least 3 liters of fluid daily. All patients consumed the same diet and received the same ward care by a fixed personnel. Daily observation of the number of stools passed, their consistency (whether or not they contained blood or mucus) was made by the patient and tabulated on the clinical record. We were forced to rely on the patient's own stool counts.

This was necessitated by the large number of cases handled at the same time, and by the limited size of the ward staff. Inaccuracies doubtless occurred, but in general we were impressed by the meticulous accuracy with which the Chinese patients enumerated the daily number of stools passed. Whenever doubt existed as to the accuracy of the count the ward staff inspected all stools passed in a 24 hour period. If the observed number was greatly at variance with previous counts the case was excluded from the study. Whatever the inaccuracies they were presumably equally distributed in the 3 groups, and in a series as large as this could scarcely have altered the results significantly. The patients were discharged from the hospital at the earliest moment they were considered able to resume duty. In those instances where hospitalization was prolonged for other reasons a notation was made of the point at which the dysentery was no longer considered the cause of disability.

In the 4th group of patients, 50 in number, treatment was not begun immediately for reasons discussed later. They presented a subacute form of the disease and were treated with sulfaguanidine or sulfadiazine, in the dosage indicated above, after a control period without medication.

All patients admitted with the presenting symptom of severe diarrhea or dysentery obviously did not have true bacillary dysentery. The 2 commonest diseases with which it was easily confused were acute amebic dysentery and the dysenteric form of malaria. Cases of simple diarrhea, without blood or mucus in the stools, which subsided within 48 to 72 hours were occasionally assigned to the dysentery wards. All patients falling into these 3 groups were excluded from the study as soon as the proper diagnosis was established.

Results. Included in the study were 334 cases. In 25% the clinical diagnosis of bacillary dysentery was confirmed by positive stool cultures, in the remaining 75% the diagnosis was made on clinical grounds alone. [It is well known that in many cases of bacillary dysentery the bacteria may not be recoverable after the first few days.—Ed.] The latter group were in every

respect similar to those in which the diagnosis was bacteriologically verified, and other possible causes of dysentery were excluded. No doubt existed in our minds that these patients were in fact suffering from true bacillary dysentery in spite of a single negative stool examination. Of the 334 cases 284 had an acute form of the disease and were divided into 3 groups, for immediate treatment as follows: 105 were controls receiving only a placebo, 75 received sulfaguanidine and 104 sulfadiazine. In each of these 3 groups the number of cases with positive stool cultures was almost identical. A smaller group of 50 received one or the other drug later in the course of the disease, after a control period without medication. In Table 1 are data, excluding the latter 50, showing the age of the patients, the duration and severity of the illness, the admission blood studies and temperature readings, and the incidence of intestinal helminths, which were predominantly ascaris, hookworm and trichuris. Examination of the figures confirms, we believe, our clinical impression that the 3 groups of patients were comparable in every respect. Indeed, this would be anticipated from the fact that the patients were assigned to the 3 groups in rotation, without any selection whatever.

Chart 1 contains a graphic representation of the average daily stool counts in each of the 3 groups. The control group, with an initial average stool count of 15 per 24 hours, appears to have had a slightly more severe form of infection. Even so, the rate of subsidence of the dysentery was entirely comparable to that in the treated cases, and by the end of 1 week the average stool counts in all 3 groups were identical. It is clear that the sulfonamides did not materially reduce the frequency of the stools.

In Table 2 are data which indicate that the febrile phase of the disease was not influenced by the administration of a sulfonamide nor was the period of hospitalization shortened. All groups gained equally in weight. It is our distinct clinical im-

pression that in the untreated cases symptoms and physical signs subsided as rapidly as in those who received specific medication.

Stool culture yielded a variety of dysentery organisms of which the most frequently encountered were *Sh. paradysenteriae-Flexner*, *Sh. dysenteriae* and *Sh. paradysenteriae-Hiss*. Of the positive cultures 85% fell into 1 of these 3 groups. The incidence of the various types of organism

than those in which the diagnosis was based on clinical grounds alone. In Chart 2 is a representation of the average daily stool counts in the treated and untreated patients with positive stool cultures. Their rate of recovery, as judged by this criterion, appears to have been equally rapid, and entirely comparable to the group as a whole.

In Chart 3 are data on 50 miscellaneous cases which were not, for one reason or

TABLE 1.—CLINICAL AND BLOOD DATA IN CONTROLS AND THE SULFONAMIDE TREATED GROUPS

	Control group	Sulfaguanidine group	Sulfadiazine group
Av. age (yrs.)	27	29	27
Av. duration of symptoms prior to admission (days)	5.2	5.0	5.4
Severity of illness:			
1. Slightly	56%	53%	69%
2. Moderately	42%	41%	29%
3. Severely	2%	6%	2%
Av. temperature on admission	99.4°	98.6°	98.4°
Av. maximum temperature during hospitalization	100.4°	100.4°	100°
Positive stool cultures	30%	34%	24%
Av. WBC count on admission	8400	8400	7600
Av. Hb. on admission (gm.)	14.6	13.8	14.0
Intestinal parasitism	25%	25%	31%

TABLE 2.—DURATION OF FEVER, HOSPITALIZATION AND MEDICATION AND GAIN IN WEIGHT IN 3 GROUPS

	Control group	Sulfaguanidine group	Sulfadiazine group
Av. febrile hospital days	2	2	2
Av. period of hospitalization (days)	12	13	12
Av. weight gain (pounds)	5	6	5
Av. days of medication	0	9	6

TABLE 3.—TREATMENT GROUPS ACCORDING TO DIFFERENT TYPES OF SHIGELLA

	Control group	Sulfaguanidine group	Sulfadiazine group
Total number of cases with positive stool cultures	24	23	22
Organism:			
<i>Sh. paradysenteriae Flexner</i>	14	13	8
<i>Sh. dysenteriae</i>	5	5	3
<i>Sh. paradysenteriae Hiss</i>	2	2	7
<i>Sh. paradysenteriae Sonne</i>	1	2	2
<i>Sh. paradysenteriae Strong</i>	2	1	1
<i>Sh. dispar</i>	0	0	1

in the control and treated series was roughly comparable (Table 3). It will be observed from Table 1 that the percentage of positive stool cultures was relatively low, from 25 to 34%. This is probably to be expected in view of the fact that only a single culture was obtained, and this, on the average, 6 days after the onset of symptoms. It was of interest to determine whether the bacteriologically proved cases were more susceptible to the sulfonamides

another, acceptable in the larger groups just described. They represent, in part, cases in which treatment was delayed either because of uncertainty in diagnosis or the presence of complicating diseases such as malaria. Some were transferred to the dysentery wards late in the disease, others had received previous medication, still others had relapsed after an initial improvement with or without treatment. This group, on the average, was admitted

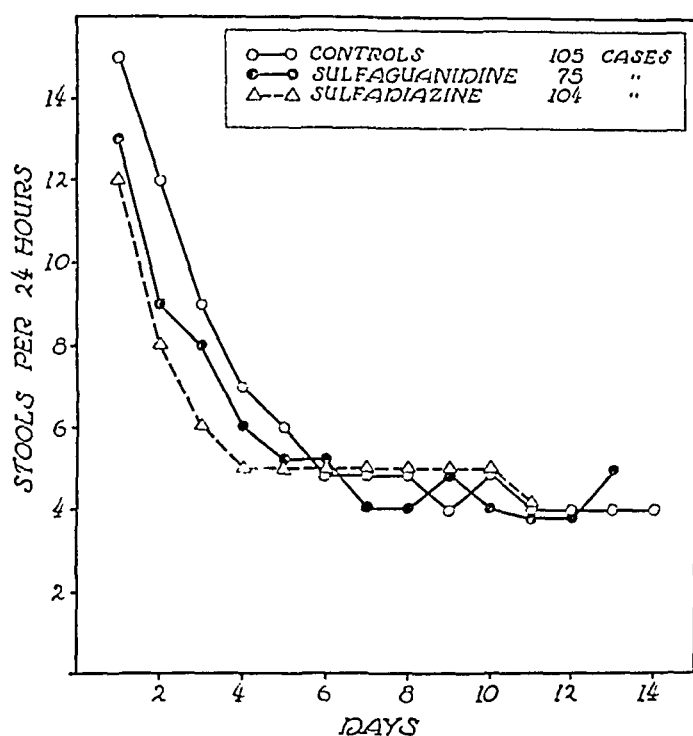


CHART 1.—The average daily stool counts in the control and sulfonamide treated patients.

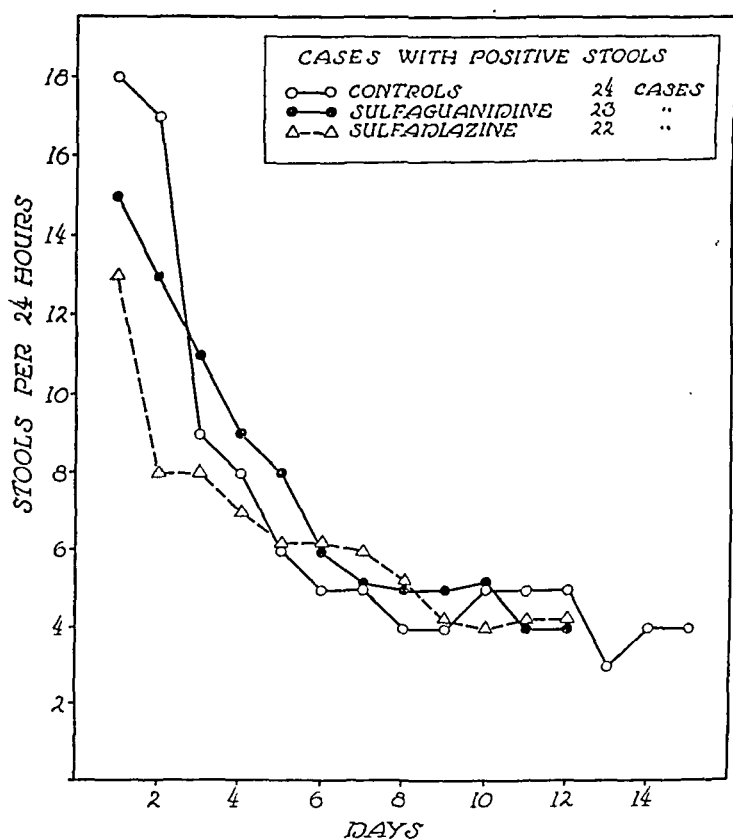


CHART 2.—The average daily stool counts in the control and sulfonamide treated patients with positive stool cultures.

to the hospital on the 8th day of the disease, only 20% had positive stool cultures, and treatment with a sulfonamide was begun on the 18th day of the disease, and continued for 8 days. While the group is made up of subacute, chronic and atypical forms of the disease rather than the classical acute type of bacillary dysentery, the results of therapy seem worth recording since such cases were frequently encountered. It would appear that both drugs, especially sulfaguanidine, reduced the stool counts somewhat, but the effect was not an impressive one.

while in 1 urine flow was reestablished spontaneously after the liberal administration of parenteral fluids.

Mortality. No deaths occurred in the cases reported here. Only 1 case has terminated fatally in our entire experience. This was a patient with a choleraic form of the disease who died very shortly after admission and who was thought to have, in addition, typhus fever.

Discussion. A critical examination of our data has failed to provide us with evidence that the clinical course of acute bacillary dysentery was significantly af-

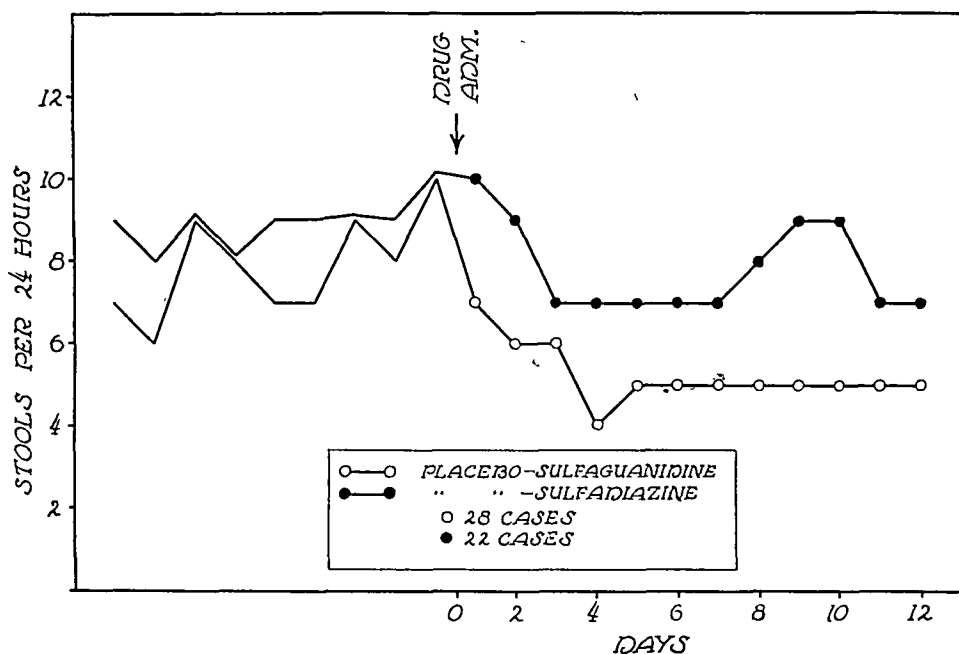


CHART 3.—The average daily stool counts of patients receiving sulfonamide therapy after a preliminary period without medication.

Complications of Sulfonamide Therapy. No untoward reactions to sulfaguanidine were observed. In 10 instances gross urinary complications were encountered in the cases receiving sulfadiazine. Hematuria occurred most frequently, costo-vertebral angle pain, dysuria, oliguria and anuria were complained of in descending order of frequency. Three patients receiving sulfadiazine became totally anuric for from 3 to 5 days; they developed azotemia, severe costo-vertebral angle pain, and vomiting. They appeared to be in critical condition. Two required ureteral lavage,

affected by the administration of either sulfaguanidine or sulfadiazine. They produced no discernible amelioration of symptoms, nor subsidence of positive physical findings. The progressive decrease in the number of daily bowel movements appeared to be essentially equal in both treated and untreated groups. The febrile phase of the disease lasted on the average only 2 days after hospitalization regardless of the method of treatment. The duration of illness, an all-important military consideration, was not reduced by the administration of a sulfonamide.

These results are so at variance with the experience of most other observers that the reasons for their divergent nature require consideration. The first possible explanation lies in the fact that the treatment was begun, on the average, 5 days after the onset of symptoms. This was relatively late in the course of a disease, which, untreated, usually lasts only 2 weeks. It is well recognized that dysentery organisms tend to disappear quite rapidly from the stools of untreated cases, and it is reasonable to assume that unless therapy is begun early little beneficial effect can be expected. The failure to observe favorable effects from sulfonamide therapy cannot, however, be wholly attributed to its relatively late administration, for many of our patients were treated initially on the 1st or 2nd day of the disease. An analysis of the result of therapy in this group gave no indication that it was superior to that which was begun on the 5th day of the disease.

A second possible explanation for our negative results could rest on the fact that we were dealing with such a mild form of the disease that the beneficial effects of drug therapy were difficult to measure in objective terms. It is apparent that we were dealing with a relatively mild form of dysentery since our mortality was *nil* and only 10% of our patients were regarded as seriously ill. This differs widely from the picture described by others, especially of epidemics in wartime. The mortality from the disease in the United States is approximately 5% and in 6 states between 1933 and 1937 it was 15.7%.² This possible explanation however does not appear to us to be adequate. It would be misleading to imply that our cases were so mild that amelioration of their clinical condition could pass undetected. For even the cases classed as mild had marked abdominal pain, dysentery, and frequently were febrile, prostrated and occasionally in mild shock. The disease required 10 to 14 days to run its course, and it is inconceivable to us that a significantly beneficial

effect from drug therapy could have escaped unnoticed.

It is unfortunate that the conditions under which these observations were made were such that it was not feasible to obtain more than a single stool culture in each case. The percentage of bacteriologically proved cases of bacillary dysentery would undoubtedly have risen with more intensive bacteriologic study. However in our opinion this limitation is not serious for 3 reasons, first, because the result of our study in the clinically diagnosed group was identical with that in the substantial group of bacteriologically proved cases, second because of our conviction, after an extensive experience with the disease, that the former group were, in fact, true cases of bacillary dysentery; and finally, because the patient with acute dysentery but with a negative stool culture presents precisely the same clinical and therapeutic problem as does the patient with a positive culture.

A parenthetical comment concerning the relative virulence of the organisms in the dysentery group deserves mention. It is generally held that *Sh. dysenteriae* produces a more severe form of the disease than do the other organisms in the dysentery group. This has not been our experience. An attempt was made to predict, on the basis of the severity of the clinical manifestations, what type of organism would be isolated on stool culture. We were totally unable to demonstrate that *Sh. dysenteriae* produced a more fulminating form of the disease than did other organisms of the genus *Shigella*.

With respect to the toxic effects of the sulfonamides we observed no ill effects from the administration of sulfaguanidine. However, the renal complications from the use of sulfadiazine were rather frequent and, in several instances, alarming. This is scarcely to be wondered at in a disease of which dehydration may be a feature and in a locality where very high temperature prevails, and under circumstances in which meticulous attention to fluid intake and urinary sediment were not pos-

sible. In all probability we would have had 2 fatalities from ureteral blockage if facilities for ureteral lavage had not been available. In the conditions which prevailed during this study it was our impression that the danger of sulfadiazine in the dosage administered exceeded that of the disease for which it was employed.

We wish to emphasize the fact that these observations relate only to the effects of sulfadiazine and sulfaguanidine on the clinical course of acute bacillary dysentery, and in no sense cast doubt on the advisability of the administration of these drugs to reduce the carrier rate following the acute stage of the disease. It has been amply demonstrated by various observers^{1,3,4,6} that the incidence of positive stool cultures during and following the disease can be materially reduced by the administration of sulfonamides. Unfortunately the conditions under which our observations were made did not permit studies on the carrier rate or relapse rate in our cases. But the observations of others have

demonstrated conclusively that these can be substantially reduced by doses of the sulfonamides which are smaller than those now recommended for treatment of the acute stages of bacillary dysentery. However our experience has convinced us that the desirability of administering these drugs is dictated by public health considerations rather than by the immediate clinical benefit which may be anticipated.

Conclusions. The efficacy of sulfaguanidine and sulfadiazine in the treatment of acute bacillary dysentery has been studied in approximately 300 Chinese soldiers in India. Neither drug shortened the course of the disease, ameliorated the symptoms nor altered the eventual outcome. The danger of renal complications following the administration of sulfadiazine in our opinion contraindicates its use in the dosage employed under the conditions which prevail here. These observations do not apply to the demonstrated value of these drugs in reducing the carrier rate following acute bacillary dysentery.

The authors wish to express their indebtedness to 1st. Lt. M. M. Carroll, A.N.C., for her invaluable assistance in the care of the patients, in the conduct of the experimental observations and in the compilation of the data, and to Tech. 3 Tony Di Francesco for his efficient conduct of the dysentery wards.

REFERENCES

1. CORNELL, V. H., WATT, J., and DAMMIN, G. J.: *Mil. Surg.*, **92**, 253, 1943.
2. FELSEN, J.: *In Diseases of the Digestive System*, Portis, Phila., Lea & Febiger, p. 813, 1941.
3. HARDY, A. V., BURNS, W., and DE CAPITO, T.: *Pub. Health Rep.*, **58**, 689, 1943.
4. HOAGLAND, R. J., HARRIS, F. H., and RAILE, R. B.: *War Med.*, **4**, 400, 1943.
5. NETER, E.: *Gastroenterol.*, **1**, 471, 1943.
6. ROBERTS, T. L., and DANIELS, W. B.: *J. Am. Med. Assn.*, **122**, 651, 1943.

PROGRESS OF MEDICAL SCIENCE MEDICINE

UNDER THE CHARGE OF
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INFECTIOUS POLYNEURITIS (GUILLAIN-BARRÉ SYNDROME)

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THE recent discussions of acute anterior poliomyelitis, stimulated by the introduction of the Kenny method of treatment, and the widespread prevalence of the disease during the season of 1944 have aroused interest in the Guillain-Barré syndrome because the latter enters into the differential diagnosis of poliomyelitis. Whether the Guillain-Barré syndrome may be classed as a distinct entity, as most recent writers believe, or whether it represents a variation of poliomyelitis due to diverse causes cannot be stated at present. One clinical fact emerges from the mass of data concerning both entities: The Guillain-Barré syndrome bears a far more favorable prognosis than does poliomyelitis. That fact in itself is justification for inclusion of the Guillain-Barré syndrome in the diagnostic possibilities of any despondent, acutely ill, paralyzed patient.

The diagnosis of the Guillain-Barré

syndrome is based on the clinical picture, the albuminocytologic dissociation of the spinal fluid, and the progress of the illness. In view of the fact that the etiology and true nature of the disease remain obscure, the disease yet constitutes a syndrome in the true sense. Probably few diseases in clinical medicine possess as many appellations as does this entity. The more commonly employed synonyms in the American literature are listed.* No term is entirely applicable. As will be evident in a moment, there is little proof that the disease is *infectious* or *infective*. Neither is it always *febrile*, and in some instances it cannot strictly be said to be *acute*. Upon close analysis the term *neuritis* differs little in meaning from *neuritis*. Descriptive terms, such as *ascending*, *facial diplegia*, *albuminocytologic dissociation*, while correct in some cases, do not suffice to indicate the protean manifesta-

* Acute febrile polyneuritis; infective polyneuritis; acute polyneuritis with facial diplegia; myeloradiculitis; polyradiculoneuritis; acute infectious neuronitis; radiculoneuritis; acute benign infectious myelitis; meningoradiculomyelitis; encephalomyeloradiculitis; Guillain-Barré syndrome; Guillain-Barré-Strohl syndrome; facial diplegia with polyneuritis; myeloradiculoneuritis; acute ascending paralysis; infective neuronitis; radiculoneuritis with acellular hyperalbuminosis of cerebrospinal fluid; acute infective polyneuritis; polyneuronitis; motoneuronitis; Landry's ascending paralysis; acute infective meningomyeloneuritis; acute toxic polyneuritis; polyneuritis of unknown etiology; acute ascending necrotic myelitis.

tions of the disease. The term *motoneuronitis* connotes little in the clinical sense. Other terms, or combinations of terms, are based upon the assumed pathology of the disease and again disregard the paucity of our knowledge of this entity as well as the visceral pathologic changes recently described by Sabin and Aring.⁵¹ Use of Landry's name in connection with this disease would have sufficed if Landry's original case³⁶ had been proved. Recently Brown⁷ has contended it was nothing more than polyneuritis of beriberi following starvation in an acute infection. The names of Guillain and Barré are closely linked with this syndrome. It is by this latter appellation that the disease is best known both in the American literature and in the foreign reports. Certainly they can be credited with first discerning the albuminocytologic dissociation of the cerebrospinal fluid²⁶ as well as with a recent comprehensive review of the subject.²⁵

Historical Comment. Osler,⁴⁴ in 1892, rendered the first lucid description of this entity under the name of *acute febrile polyneuritis*, and pointed out the difficulties in distinguishing between this entity and Landry's ascending paralysis. In 1898 Mills⁴² introduced the term *neuronitis* to designate involvement of the entire neuron by the pathologic process. Buzzard,⁸ in 1907, reported several cases under the caption of *acute toxic polyneuritis*, and Laurans³⁷ in the following year commented on the occurrence of facial diplegia in the course of *infectious polyneuritis*. In 1916, Patrick⁴⁵ reported 2 cases of facial diplegia in patients with multiple neuritis and thus focused additional attention on the possibility that the 7th or another cranial nerve might be involved in this disease. In the same year Guillain, Barré and Strohl²⁶ recognized the high protein and low cellular content of the cerebrospinal fluid (albuminocytologic dissociation) and emphasized the equally significant fact that the prognosis was favorable.

Holmes,³¹ in 1917, reported the clinical picture as seen in 12 patients together with the pathologic findings in 2 of them.

Holmes used the term *acute febrile polyneuritis* to designate the disease. A year later, Bradford, Bashford and Wilson⁶ published a comprehensive monograph on the subject and summarized the observations of 30 cases. Most of the cases reported by Bradford manifested involvement of the facial nerve and the cerebrospinal fluid was considered normal in each patient. His series disclosed a mortality of 26.6% and he noted that the patients remained remarkably free from cerebral or mental symptoms even *in terminus*. Bashford discussed the pathologic anatomy of the disease both in man and in the monkey and thought that the pathologic process in both was similar. He likewise thought that he could transmit the disease from man to monkeys as well as from monkey to monkey by subdural inoculations of glycerin emulsions of the involved spinal cord. Wilson went so far as to advance the belief that the causative organism was a virus which he could cultivate from the affected spinal cords of both man and monkey. Arkwright,³ in 1919, definitely disproved this theory by showing that the globoid bodies which Wilson and his associates had recovered were contaminants.

In 1919, Foster Kennedy³⁵ reported 4 cases and chose to reintroduce the term *neuronitis*. Summarizing the observations of cases occurring among the troops of World War I, Casamajor⁹ suggested the term *acute infective meningomyeloneuritis*. The spinal fluid examinations in his cases were within normal limits.

Recognition of the disease followed rapidly thereafter. Viets,⁶⁰ in 1927, reported 2 cases and described the pathologic findings in 1. Both of his cases had facial diplegia and albuminocytologic dissociation. Collens and Rabinowitz,¹² in 1928, reported an instance of polyneuritis with facial diplegia occurring 3 weeks after an episode of mumps. They observed in their case a high protein content of the cerebrospinal fluid without cells and collected 4 similar cases from the literature. In 1934, Urquhart⁵⁹ reported an instance

of the disease which followed the onset of measles by 1 week. These and similar observations that the disease is preceded in a substantial percentage of the cases by an upper respiratory infection have served to focus attention on a possible infectious, perhaps viral, origin of the disease. Because of the desirability of the differentiation of the disease from acute anterior poliomyelitis, increasing reports concerning sporadic cases have appeared in both the American and foreign literature. For comprehensive reviews of the subject the reader is referred to the papers of Guillain,²⁵ Gilpin, Moersch and Kernohan,²³ Hecht,²⁸ Roseman and Aring,⁴⁸ Sabin and Aring,⁵¹ Forster, Brown and Merritt,¹⁶ Fox and O'Connor,¹⁷ and Hatoff.²⁷

Etiology. Most writers agree that this syndrome is probably infectious and viral in origin. Proof for this assumption, however, has not been forthcoming. We have already cited the efforts of Bashford and Wilson⁶ to isolate an organism from the involved spinal cords of their cases. Arkwright³ and later Sabin and Aring⁵¹ have disproved their findings; in fact, in an addendum to Arkwright's paper, Bashford and Wilson retracted their original statement. To date no one has succeeded in culturing an organism from the affected spinal cords or viscera of patients with this disease or in transferring the disease to animals. Sabin and Aring⁵¹ have reviewed their unsuccessful efforts to produce the disease in mice, guinea-pigs, rabbits and monkeys. It is of interest that Cobb and Coggeshall¹¹ believed the necropsy findings of the few patients that had been studied to be compatible with a virus infection of the central nervous system, a view which has been accepted in most part by later investigators. The evidence, therefore, concerning the etiology of this condition remains presumptive.

Beginning with Osler, most writers have emphasized either the infectious type of onset of this disease or the relationship of this condition to an antecedent infection. In a review of the literature, Fox and

O'Connor¹⁷ found that 49 of 122 cases had a history of a preceding illness, such as coryza, aches and pains, and gastrointestinal disturbances. Each of their 4 cases had an infection of the upper respiratory tract prior to the onset of paralysis. Each of the 3 patients that we are reporting herein likewise had an upper respiratory type of clinical picture at or prior to the onset of this condition. As a rule, the infection precedes the onset of the disease by a week or more but may be present when neurologic symptoms develop. Thus, a latent period between the preceding infection and the development of neurologic manifestations may or may not be demonstrable.

The type of infection initiating this trend of events varies considerably. The syndrome has been known to be precipitated by or supervene in systemic infections²⁷ such as encephalitis, measles, diphtheria, mumps, mumps complicated by orchitis, mastitis, scarlet fever, influenza, pneumonia,⁴⁸ chicken-pox, botulism and syphilis, and recently infectious hepatitis. Hiller and Fox³⁰ have recently noted the association of this entity with infectious mononucleosis and suggest that a heterophil antibody determination be obtained on every patient with the Guillain-Barré syndrome. In addition, coexistence of this disease has been noted with various foci of infection: Vincent's angina, tonsillitis, dental caries and abscessed teeth, perianal abscess, osteomyelitis, epidural abscess and furunculosis. Primary development of the disease without preceding infection can be demonstrated in a small percentage of cases.

As previously stated, the inciting organism has not been established nor are the mechanisms clear by which this syndrome results from such a diversified group of unrelated infections. The weight of opinion leans toward the viral origin of this disease and it is thought that a neurotropic virus^{23,51} is in some way activated by the antecedent infection. Whether such a virus is already present in the central nervous system or whether it is

introduced by the associated infection remains obscure. Other organisms have received consideration as active causes for this entity, particularly staphylococci,⁵ streptococci^{38,49} and *Hemophilus influenzae*.⁵ In such instances the toxic etiology, as suggested by Heernu²⁹ and Sabin and Aring⁵¹ offers the most satisfactory explanation for the neurologic phenomena. Such a circulating toxin may be elaborated by the microorganisms producing the respiratory infection and possess an affinity for the peripheral as well as the central nervous system and viscera. Sahs and Paul,⁵² on the other hand, state that the available evidence points primarily to an intoxication of the peripheral nervous system rather than to an actual infection.

In a syndrome in which a definite incriminating factor cannot be demonstrated and in which the pathologic changes may vary widely, it is, of course, logical that other causes for this clinical picture may be found. In other words, this syndrome may be secondary to some entity of greater importance. Among these are serum sickness,⁴³ sulfonamide intoxication,^{27,39} tuberculosis,²⁰ leprosy,^{18,46} cervicodorsal arthritis, diphtheria, diabetes,⁴⁶ and artificial fever.²¹ The resemblance to myasthenia gravis has likewise been emphasized. Thus, patients with this entity should be studied carefully to exclude demonstrable organic disease both in the central nervous system and elsewhere throughout the body. Careful inquiry into the medical history as to dietary deficiencies and assimilation of heavy metals such as lead, mercury or other noxious agents is likewise indicated from the etiologic point of view. Suffice it to say that the more careful the diagnostic investigation, the fewer cases of primary origin will be revealed.

Little information concerning the etiology of this condition has been derived from the clinical incidence. As a matter of fact, it is difficult to obtain any satisfactory values for the incidence of the disease. The large number of synonyms

employed renders an analysis of the literature or hospital records almost fruitless. Gayle and Groom²² estimated in 1943 that probably 50 cases of this entity had been studied, but Fox and O'Connor¹⁷ 1 year earlier collected 122 cases from the literature and since their report several papers on this syndrome^{1,2,4,10,13-15,19,22,27,30,33,34,43,47,50,52-55,61} have appeared in the American literature, not to mention foreign reports. That the disease is sporadic and seldom epidemic seems true although recent observations suggest that mild epidemics may occur. Reports vary concerning the seasonal incidence but the bulk of the evidence indicates that the greatest incidence occurs during the variable weather of the cold seasons, a time during which acute anterior poliomyelitis is not likely to attain its maximum distribution. It shows equal predilection for both sexes and for all age groups. So many cases have been described in the age groups less than 20 years that Susman and Maddox⁵⁷ termed this entity an apyrexial disease of childhood and adult life. It is of interest to note that Brown⁷ believed that this disease as a disorder of the nervous system is exceeded in incidence only by alcoholic polyneuritis.

Some have considered this disease as abortive poliomyelitis. Others distinguish between the 2 conditions on the basis of the clinical picture. The points in differentiation have been considered in detail in the section on Diagnosis.

Morbid Anatomy. The pathologic changes of this entity have been studied by Holmes,³¹ Bradford, Bashford and Wilson,⁶ Casamajor,⁹ Viets,⁶⁰ Greenfield and Carmichael,²⁴ Gilpin, Moersch and Kernohan,²³ Sabin and Aring,⁵¹ Honeyman,³² and Roseman and Aring.⁴⁸ Although the earlier writers devoted their attention chiefly to the pathology of the nervous system both centrally and peripherally, the later writers, particularly Sabin and Aring and Roseman and Aring, have emphasized the visceral changes as well, which indicate the protean manifestations of this disease. The pathologic alterations

of the nervous system will be summarized first. In general, there is macroscopically a moderate degree of edema of the brain, spinal cord, and peripheral nerves with slight vascular congestion of the overlying *leptomeninges* of the brain and spinal cord. Fairly uniform changes may be found in the peripheral nerves. These consist microscopically of marked edema of the bundles, congestion, focal infiltration of inflammatory cells, swelling and beading of the myelin sheaths, and fragmentation, beading and dissolution of the axis cylinders. Involvement of the gray columns of the cord may be found in nearly all cases with the most marked changes at the cervical and thoracic levels. The anterior horn cells likewise show varying changes including widening of the perineuronal spaces, chromatolysis, and vacuolization of the cytoplasm. Changes of a similar nature may be found in the other fiber tracts of the cord and brain stem. In some instances the morbid process appears diffuse, in others spotty, and in a few cases scant or no changes can be demonstrated. In the cerebrum and cerebellum, the abnormalities have been described as slight "outfall" of nerve cells, shrinkage of the ganglion cells with poor staining qualities of both the cytoplasm and nuclei, congestion, swelling of the oligodendroglia of the white matter, and slight inflammatory reaction of the meninges.

It seems clear that the pathologic changes described above are more severe in the peripheral and cranial nerves. Indeed, the changes in the central nervous system may be interpreted as mild in character and perhaps secondary to those of the peripheral nervous system. That these changes are readily reversible likewise appears evident. One point is worthy of emphasis as support for this statement: Neuronophagia is relatively rare in the brain and spinal cord as compared to the marked degree of phagocytic reaction in the peripheral nervous system. The Nissl substance is likewise well preserved

centrally as contrasted to dissolution peripherally.

Sabin and Aring⁵¹ have summarized the visceral manifestations of this syndrome. Briefly these consist of acute passive congestion and toxic changes of the liver, kidneys, heart and spleen. Some fatty infiltration of the liver may be noticeable about the central vein areas. The adrenal gland in 1 of their cases revealed widespread softening on gross examination, whereas the microscopic studies disclosed significant abnormalities in the adrenals of all cases. These consist chiefly of patchy areas of degeneration, infiltration with plasma cells and lymphocytes and vacuolization. The lungs revealed bronchitis in all their cases with some patchy lobular pneumonia, varying areas of atelectasis and compensatory emphysema. The visceral changes are of such a character as to resemble closely the changes in typhoid fever and diphtheria in which a circulating toxin may be held responsible. In fact, Sabin and Aring have compared these changes to those produced by a pantropic virus. These changes, in view of the etiologic relationships discussed previously, point strongly to the microorganisms found under certain conditions in the upper respiratory tract as causative factors. Proof that these pathologic findings may be produced by the toxins elaborated by these organisms has not been demonstrated but the theory does open a trend for additional investigation.

Clinical Picture. In a syndrome characterized by widely divergent precipitating factors and resulting in atypical, varied pathologic changes, it is remarkable that the clinical picture is as clearly defined as it is. In their original paper purporting to present a new syndrome, Guillain, Barré and Strohl²⁶ outlined what they considered to be the typical course of the disease. Guillain²⁵ has recently amplified this description of the clinical picture. Not all writers are in entire agreement with Guillain, particularly with regard to his belief that all cases must present albuminocytologic dissociation of

the cerebrospinal fluid and that all cases recover. With minor exceptions, however, the clinical picture seems to be fairly characteristic. We shall, therefore, present a composite picture of the disease as it is described in the literature.^{1,2,4,10}
13-15,17,19,27,33,34,43,47,48,50,52-55,61

As discussed previously, the onset is usually heralded by some upper respiratory infection in the form of a cold, grippe or influenzal syndrome. Mild generalized aches and pains, usually most pronounced in the calves of the legs and in the back, are frequent prodromata, as is headache. The latent period intervening between the symptoms of infection and the appearance of neurologic manifestations may vary from a few days to several months, averaging 1 to 3 weeks. The earliest neurologic symptoms are usually referable to the sensory system. The pain in the back and legs may be confused with rheumatism or lumbago, but occasionally the pain may be of such severity as to require sedation. Muscle and nerve tenderness are invariably present. Paresthesias, particularly numbness of the hands or feet, are frequent. Characteristically, the sensory disturbances are limited to the distal portion of the extremities and diminish in severity as one advances proximally. Objective sensory disturbances may be elicited shortly after the onset as denoted by impairment of vibratory sense and diminished perception of pain and light touch.

In general the motor disturbances appear any time within a few hours to as long as 1 week after the onset of the sensory phenomena and may develop insidiously or rapidly. The motor disability is usually bilateral, symmetrical and progressive. In contrast to the sensory disturbances, the motor signs are more striking in the proximal than in the distal musculature. Once developed, the motor disturbances completely overshadow the sensory changes. A flaccid paralysis ensues which may progress to quadriplegia. Both the rapidity and the degree of paresis vary considerably from

slight muscular weakness and awkwardness to complete helplessness in a patient in whom all voluntary movements have been lost except for a slight wriggling of the fingers and toes. These changes may develop within a few days or require weeks to attain the full blown picture with occasional periods of remission. Additional generalizations are permissible: Wasting or atrophy of muscle segments seldom occurs except that induced by disease; fibrillary movements are seen infrequently; involvement of the trunk, intercostal muscles, or diaphragm renders the outlook exceedingly grave.

Other neurologic manifestations are not characteristic. The tendon reflexes are either diminished or absent. The abdominal reflexes may be diminished or unaffected. No pathologic reflexes can be elicited. The sensory disturbances, namely impairment in the sense of vibration and diminished perception of pain and light touch, have been mentioned. Involvement of the rectal or vesical sphincters occurs only rarely, except in children and in the moribund. Cranial nerve involvement occurs in a high percentage of cases. Bilateral or unilateral facial paralysis is frequent and is often overlooked in the bilateral types. This is nuclear or infranuclear in origin so that the brow and eyelids are involved as well as the lower portion of the face. Other cranial nerve involvement may be manifested by blurring of vision, nystagmus, palatal paralysis, dysphagia, dysphonia, difficulties in mastication, anosmia, deafness, tinnitus, vertigo, lingual deviation, and impaired taste. Papilledema and optic neuritis may be found infrequently. Pediatricians writing on this subject have stressed the euphoric state of children⁵⁷ but in adults and the more severely ill, depression or delirium are more common.

Though the disease does affect the viscera, as determined by postmortem examinations, constitutional or systemic manifestations other than those discussed above are infrequent and usually mild in character. The temperature seldom ex-

ceeds 102° F. and that elevation occurs usually in the 1st week of the illness. A mild tachycardia is noted in the majority of patients even in the absence of fever, although it is increased proportionately to the temperature elevation when such occurs as well as in the dangerously ill patients. Other symptoms are rarely present except as complications resulting from the original or secondary infections, such as pneumonia. McIntyre⁴⁰ has recorded electrocardiographic evidences of a toxic myocarditis in a patient with this syndrome.

Course and Prognosis. The course of the illness is quite variable. In general the duration may be stated to vary from 2 weeks to 3 years or more. Convalescence is usually slow and, as a rule, recovery of function follows the same order in which it was lost. Occasionally recovery is rapid and progressive as in Case 1 of our patients. Some patients never regain a complete sense of well-being and vigor. Others manifest only slight residual defects such as weakness of one side of the face. Still others (Case 2 of our group) have paralytic phenomena as long as they have been observed. By the original postulates of Guillain, Barré and Strohl,²⁶ and later Guillain,²⁵ recovery should occur in every patient for the disease in question to be compatible with their syndrome. Whether they were dealing with a benign form of the disease in their series of patients or whether the diagnoses in the patients of other investigators, including Case 2 of our group, were incorrect, cannot be answered in the present state of our knowledge. Certainly the preponderance of opinion indicates that this syndrome is not at all as benign as Guillain and his group believed. Those observers with large groups of patients to evaluate report varying statistics concerning the mortality rate. Thus Gilpin, Moersch and Kernohan²³ recorded 14%; Roseman and Aring,⁴⁸ 18.8%; and Forster, Brown and Merritt,¹⁶ 42%. In a survey of the literature as a whole, Fox and O'Connor¹⁷ concluded that the mor-

tality rate was approximately 20%. Death occurs within the first 2 weeks of illness and may be attributed in most part to respiratory paralysis. Recurrences of the disease have not been observed.

In general the prognosis is uniformly good in children. In adults the involvement of the intercostal muscles, abdominal musculature and diaphragm seriously affects the prognosis. It has been the experience of most writers that recourse to the respirator bears grave prognostic significance. Immediate recognition and correction of any accompanying disease or foci of infection, of course, improves the prognosis. Other than these factors, little of prognostic value can be learned from the individual patient.

Diagnosis and Differential Diagnosis. In the diagnosis of this condition much weight is given the laboratory findings of the cerebrospinal fluid. In their original paper, Guillain, Barré and Strohl²⁶ described the elevated protein content of the cerebrospinal fluid with no increase in cellular content (albuminocytologic dissociation) and these findings have been adhered to by the French writers and others as essential features of the diagnosis. In fact, Guillain²⁵ flatly stated that the protein determination must exceed 300 mg. to fit this syndrome. Whereas an elevation of the protein content of the cerebrospinal fluid does occur in most instances, this is by no means invariably so nor does it indicate definitely the existence of this syndrome. From recorded cases in the literature it would appear that the protein values may range from 70 to 800 mg. or more (Case 3). In general, the elevation of the protein occurs during the acute phase of the illness, usually within the first 2 weeks. Stone and Aldrich⁵⁶ have reported 2 cases in which the determinations were rather low at the onset of the illness but attained higher values as the disease pursued its course (7th and 14th days, respectively). We observed similar findings in Case 2. Once established, the elevated protein content may persist for several years.

Roseman and Aring⁴⁸ report 1 patient whose spinal fluid protein determination had been elevated throughout 5 years of observation.

Other spinal fluid findings are usually within normal limits. The fluid is characteristically clear, xanthochromia being observed but rarely. The Pandy test for globulin is usually positive. The cell count generally reveals either an absence of cells or a slight increase up to 25 cells, all of which are lymphocytes. The spinal fluid pressure is usually normal or slightly elevated, varying as a rule from 150 to 220 mm. of water. The colloidal gold curve is generally low and non-specific.

As stated, the interpretation of the elevated protein content of the cerebrospinal fluid without a cellular response is a moot question. There is scarcely a chronic disease of the central nervous system which does not manifest an elevated protein (albumin) value at some time throughout its course. Thus, an albuminocytologic dissociation may be observed occasionally in poliomyelitis although the protein values do not usually attain the high levels observed in the Guillain-Barré syndrome.

Postdiphtheritic polyneuritis may be differentiated by the clinical history and by smears and cultures of the nose and throat. Syphilis may be excluded by the colloidal gold curve and by blood and spinal fluid Wassermann reactions as well as by other clinical stigmata of this disease. Muscular atrophies and dystrophies seldom provoke an acellular hyperalbuminosis and then only to a mild degree (100 mg. of protein or less). Tumors of the central nervous system offer more difficulty; alterations in pressure relationships and changes in the motor and sensory responses may be evident and permit localization of the growth. These examples will suffice to indicate that the cerebrospinal fluid findings must be interpreted with the history and clinical picture at hand before a correct diagnosis can be made. As emphasized by Cobb and Coggeshall¹¹ and later by Merritt and Fremont-

Smith,⁴¹ the cerebrospinal fluid may be entirely normal. Figures vary but Merritt and Fremont-Smith found normal protein values in 8 of 30 patients with this syndrome.

Other laboratory findings are non-contributory. There is usually a mild leukocytosis, the white blood count varying from 10,000 to 15,000 cells with a mild increase in polymorphonuclear cells. The urine generally reveals normal findings, though occasionally a transient albuminuria may be detected.

As discussed under the etiology of this condition, the diagnosis is permissible only when other contributing factors, such as dietary insufficiency, alcoholism, poisoning by lead, mercury or other heavy metals, and the like, can be excluded.

In other words, the syndrome must be a primary condition or the polyneuritis must be of unknown etiology in order to establish this diagnosis.

Differentiation from acute anterior poliomyelitis becomes of paramount importance. That acute anterior poliomyelitis may at times be characterized by ascending paralysis was suggested by Wickman⁶² who found such disturbances in 32 patients of 868 epidemic cases of poliomyelitis. Some of these, however, may have been instances of the Guillain-Barré syndrome for such differentiation was not made at the time of Wickman's monograph. The question arises as to whether these two entities are essentially variants of one another. The evidence is weighty on both sides of the discussion. Until more is known about the etiology and pathogenesis of acute anterior poliomyelitis as a disease entity, recognition of the Guillain-Barré syndrome as a distinct entity is warranted, if for nothing more than the better prognosis that it affords in comparison to poliomyelitis. Certainly the hope and outlook that the physician may offer the paralyzed patient with the Guillain-Barré syndrome are distinctly better than the prolonged convalescence and atrophy of the muscle groups seen in poliomyelitis. The differentiation of these two entities

has been discussed by most writers, particularly De Sanctis and Green,¹³ Sahs and Paul,⁵² and Gayle and Groom.²² It is fitting, therefore, that we summarize the differences in clinical data obtained from both groups of patients.

The essential differences are these: Acute anterior poliomyelitis has a distinct seasonal incidence, usually from August through October; the Guillain-Barré syndrome is most prevalent throughout the colder months of the year, though cases may be seen at any time. Poliomyelitis is usually epidemic; the Guillain-Barré syndrome is usually sporadic and rarely epidemic. Poliomyelitis attains its highest incidence in children during the first 2 decades of life; the Guillain-Barré syndrome occurs in all age groups with the mean average during the 3rd decade. The Guillain-Barré syndrome is preceded by an infection in more than 50% of the cases and the systemic manifestations usually subside before the neurologic phenomena appear, in which event evidences of meningeal irritation are usually inconspicuous. In poliomyelitis, on the other hand, the systemic manifestations are usually followed rapidly by signs of meningeal irritation and paralysis. Although patients with the Guillain-Barré syndrome complain of paresthesias and tenderness along the nerve trunks in variable degree, pain and muscle spasm are not nearly as marked as in poliomyelitis. Whereas the Guillain-Barré syndrome has been repeatedly described as a bilateral, symmetrical and progressive paralysis of the lower extremities with more severe involvement of the proximal group of muscles than of the distal ones, poliomyelitis may be characterized as an asymmetrical, segmental, "spotty," rarely ascending paralysis involving predominantly the hamstrings, gastrocnemius, biceps and back muscles. In 35 to 50% of all cases of the Guillain-Barré syndrome the cranial nerves, particularly the facial, are involved, usually bilaterally but occasionally unilaterally. Involvement of the cranial nerves is rare in

poliomyelitis. The spinal fluid findings in most instances of poliomyelitis characteristically reveal a moderate increase in the total protein content and a pleocytosis which is most marked in the preparalytic stages and falls rapidly once paralysis ensues. Final differentiation of the two entities will be established by the course of the illness. Patients with the Guillain-Barré syndrome may experience a slow, chronic progression of the paralysis over a period of several weeks then gradually recover, provided respiratory failure does not supervene. In poliomyelitis, to the contrary, additional involvement rarely occurs after the 2nd week of illness. Toomey⁶⁸ has stated that any patient with a massive paralysis lasting several weeks followed by recovery does not have poliomyelitis. Moreover, there are no distinct objective sensory changes in poliomyelitis such as may appear in the Guillain-Barré syndrome.

Treatment. Treatment is supportive and symptomatic. In view of the fact that this entity is self-limited and accompanied by a high degree of recovery, it is difficult to evaluate any form of treatment. In the early phases of the illness, attention should be directed toward the alleviation of pain and the maintenance of adequate fluid intake and nutrition. Nursing care is especially important, particularly for those in whom involvement of the rectal or vesical sphincters has occurred as well as for those with respiratory difficulties. Occasionally use of the Drinker respirator as well as repeated aspiration of mucus from the respiratory passages is indicated. Reassurance and the maintenance of morale becomes an important duty of the attending physician. Protective splints should be applied to prevent any undue contracture or elongation of paretic muscles. As the acute stages pass, physiotherapy in the form of active and passive exercises, hydrotherapy and massage should be instituted. The Kenny method has been employed by several investigators^{2,19,52} without any conclusive results.

Specific drugs offer little in the therapy of this condition. Numerous agents have been reported in the literature. De Mello, quoted by Hatoff,²⁷ and Roseman and Aring⁴⁸ have used vitamin B₁ intravenously. The dosages employed by the latter consisted of 50 to 100 mg. of thiamin chloride daily for a period as long as 3 weeks. The only benefits observed were relief of the sensory changes, such as pain and paresthesias, in 6 of 9 patients so treated without any effect upon the motor changes. Guillain²⁵ recommended several agents: intravenous infusion of sodium salicylate in serum with 10% dextrose, intravenous or intramuscular quinine, methenamine, or colloidal silver. Other empirical measures²⁷ include rubs with colloidal silver, ionized iodine or calcium administered by the transcerebro-medullary route, warm baths and irradiation. Plügge is reported by Hatoff²⁷ to have obtained good results with physiotherapy and electrical stimulation. According to Wolf,⁶³ prostigmin shortens the duration of lower motor neuron paralysis and should be tried in this syndrome. Correction of any contributory or accompanying disease is, of course, indicated. Certainly the physician should weigh carefully the potential hazards attendant upon the administration of any drug on an empirical basis for the therapy of this condition.

Case Reports. The following case reports, presented in detail, will illustrate the clinical picture and the difficulties in the diagnosis and treatment of this syndrome.

CASE 1. C. M., a 54 year old white male, was admitted to Charity Hospital on Oct. 18, 1943, with chief complaints of marked weakness of hands and legs and numbness of fingers and feet. He stated that he had had an acute onset of a cold and pain in his back 3 weeks previously. The cold had subsided before admission but the pain in the midline region of his back persisted. On admission, pain of a dull aching type radiated over the chest and abdomen. The onset of numbness of the hands and feet had been gradual. He had noted no fever and no tenderness.

On admission the physical examination disclosed general muscular weakness. The patient was unable to sit, stand or walk. Knee and ankle reflexes were absent but no pathologic reflexes were elicited. No sensory changes were found. The urinalysis, blood Wassermann reaction, and electrocardiogram were normal. The spinal fluid survey disclosed an initial pressure of 200 mm. of water with clear fluid, normal dynamics, less than 10 cells, 111 mg. of protein, 65 mg. of glucose, and 727 mg. of chlorides. The Kline and Kolmer tests were negative and the colloidal gold curve was 1122331000.

Therapy consisted of bed rest, nursing attention, a diet high in calories and vitamins, warm whirlpool hydrotherapy to all 4 extremities daily, and thiamin chloride in therapeutic doses by mouth. No fever was noted at any time. The patient's course in the hospital was marked by gradual and steady improvement in the motor functions of the extremities. He was discharged on Nov. 11, 1943, able to walk, stand and sit up, although ankle jerks were still missing. On December 6, the patient was seen in the clinic for a progress visit and appeared sufficiently well to resume his work.

CASE 2. A. P., a 42 year old white male, was admitted to Charity Hospital on Oct. 23, 1942, complaining of inability to void, pains in the back and chest, and numbness of both legs. He stated that he was healthy until the gradual onset of pains in the legs, arms and front of chest at night about 3 weeks previously. The following day he developed a mild cough, which was productive of a little phlegm. He remained in bed at home under the supervision of his family physician but without much change in clinical picture. Two days prior to admission to Charity Hospital, he suddenly became unable to void. His physician catheterized him the following day and he had been unable to void since without catheterization. On the day prior to admission he noted a numb sensation in his left leg. This numbness began by involving the left thigh, gradually extended to include all the left leg, so that at the end of the day he could not walk. Numbness of the perineum was noted. On the day of admission numbness also involved the right leg and extended up the trunk to a level about 1 inch above the umbilicus. The patient stated that he could move the affected parts to some

extent but could not feel them move. Bowel movements were unchanged.

Physical examination revealed a temperature of 100.2° F. Rhonchi were noted throughout the chest. Neurologic examination revealed bilateral sustained ankle clonus, impaired sensation in both legs for sharp and dull objects up to the umbilicus. Temperature sensation was unimpaired. All deep reflexes were active and equal. Abdominal reflexes were absent and Babinski reflexes were positive bilaterally.

Upon admission the urinalysis was normal and the blood revealed 65% hemoglobin, 3,900,000 red cells, 22,850 white cells (95% neutrophils, 2% lymphocytes, 1% monocytes, and 2% myelocytes). Kline and Kolmer reactions in the blood were negative on 2 occasions. Roentgenogram of the chest revealed several scattered areas of bronchopneumonia throughout the right lower hemithorax. Pneumococcus Type VI was isolated from the sputum. Treatment with 40,000 units of Type VI antipneumococcic serum and sulfadiazine was initiated. Spinal survey on admission revealed xanthochromic fluid, normal dynamics, 16 cells, mostly polymorphonuclear, per c.mm., and 4+ Pandy test. Sugar was 66 mg., chlorides were 713 mg. and total protein was 516 mg.

On October 25, a second spinal survey revealed similar findings but with absence of cells and protein of 950 mg. Tenderness was noted over the sixth dorsal vertebra. All reflexes were absent but no pathologic reflexes were elicited on October 26. Some improvement of sensibility for sharp and dull discrimination was noted.

Neurosurgical consultation was obtained on October 27 to rule out a transverse myelitis. The lesion did not progress and the level of numbness stayed at the fourth to the sixth dorsal vertebrae. Subsequent spinal tap on November 10 revealed clear fluid, pressure 200 mm. of water, normal dynamics, 2+ Pandy test, and 14 lymphocytes. Blood culture on October 24 and 26 revealed 3 to 10 colonies of *Staphylococcus aureus pyogenes*, considered a contaminant.

During his hospital stay the patient continued to run an intermittent low-grade fever up to 101.5° F. He was discharged on Nov. 28, 1943, and follow-up in December 1943 revealed no change in the neurologic picture.

CASE 3. O. T., a 31 year old, colored

male, was admitted to Charity Hospital on March 20, 1943, complaining of weakness and numbness in his legs and difficulty in voiding for 4 days prior to admission. Patient was well and vigorous until 10 days previously when he had had general malaise, generalized aching, particularly in his joints, and possibly some fever. He stopped working and went to bed, believing that he had influenza. He was apparently recovering from this episode when, 4 days prior to admission, he noted that he was having difficulty walking. He went to bed and soon noticed that he had difficulty voiding. During the intervening 4 days prior to admission the weakness and numbness of the lower extremities progressed, and finally complete urinary retention developed which necessitated hospitalization of the patient.

Upon admission to the hospital the patient stated that his vision had been growing dim, particularly in his right eye, and that his eyeballs had been somewhat painful. Physical examination revealed a well-developed, well-nourished, colored adult male who did not appear to be acutely ill and who was in no great amount of pain. Temperature was 98.6° F., pulse 80, blood pressure 148/80. Neurologic examination revealed complete paralysis of the left leg and paralysis of the right leg except that he could dorsiflex the foot and toes on the right. No atrophy or muscular fibrillations were noted. Below the second and third lumbar vertebrae there was diminution in all modalities of sensation and absence of position and vibratory sense. Reflexes were hyperactive in the lower extremities, more so on the left, but no Babinski or ankle clonus was obtained. Abdominal reflexes were absent. Spinal fluid survey revealed an initial pressure of 190 mm. of water, clear fluid, normal dynamics, 24 cells, all lymphocytes.

The following day the patient complained of increased pain in his right eye and dimness of vision of that eye. Ophthalmoscopic examination of the right eye revealed a moderately advanced papilledema involving the superior two-thirds of the disk more prominently than elsewhere. Two small capillary hemorrhages were seen on the temporal and superior temporal margins of the disk. There was constriction of the retinal arterioles with marked A-V disproportion. Examination of the left eye was

the same except for absence of hemorrhages. No muscular palsies were noted. Loss of vision continued until, 4 days later, the patient could perceive only light. On April 5, a second spinal survey revealed 130 mm. of water pressure, clear fluid, normal dynamics, 6 lymphocytes, 741 chlorides and total protein of 1140 mg. On April 6, the vision had improved sufficiently so that the patient could see fairly well. Ophthalmoscopic examination revealed regression of the previously described papilledema and resorption of the hemorrhages but A-V disproportion was still noticed.

Laboratory data were as follows: On March 28, 1943, red blood cells were 5,850,000, white blood cells 13,600 (86% neutrophils, 4% monocytes, 10% lymphocytes). On April 5, there were 5,190,000 red cells, 80% hemoglobin, 11,500 white blood cells (62% neutrophils, 1% monocytes, 37% lymphocytes). Urinalysis (retention catheter) revealed numerous white blood cells and red blood cells. Gram stain of urinary sediment showed short chain gram-positive streptococci and gram-negative rods. The Wassermann reaction was negative on 4 occasions. Blood carbon dioxide combining power was 52, urea nitrogen 10.5.

Spinal fluid on March 21 showed 777.9 mg. chlorides, total proteins 407 mg., initial pressure of 190 mm., clear fluid, normal dynamics, 24 cells, all lymphocytes. On April 5, 1943, spinal fluid survey showed

130 mm. of water initial pressure, clear fluid, normal dynamics, 6 lymphocytes, 741 mg. chlorides, 1140 mg. total protein, 46 mg. sugar. On April 12, 1943, spinal survey showed 160 mm. of water initial pressure, normal dynamics, clear fluid, 4+ Pandy test, 950 mg. total protein. On May 4, protein was 114 mg., glucose 60 mg., chlorides 743 mg., Pandy test 2+, 16 cells. On July 23, protein was 163.2 mg., glucose 53 mg., chlorides 717 mg., colloidal gold curve 0000001100.

Roentgen views of the spine on admission revealed no evidence of bone or joint disease.

The course in the hospital was characterized by an irregular low-grade fever, occasionally spiking to 102° F., for 2 months. At no time was the patient seriously ill. About the 4th week after admission decubitus ulcers on the buttocks developed and presented serious nursing problems. An indwelling catheter was left in place for almost 6 months. Therapy consisted of urinary antiseptics, urologic attention to bladder and indwelling catheter, physiotherapy consisting of massage from hips to toes, infrared irradiation, active assistive motion of joints, and sulfathiazole.

Indwelling catheter was removed on Aug. 14, 1943, at which time the patient was able to urinate spontaneously. He was discharged Aug. 18, 1943. No information concerning his recent progress has been obtained since that date.

REFERENCES

- (1.) Anderson, G. C.: *New Orleans Med. and Surg. J.*, 93, 443, 1941. (2.) Aring, C. D., and Sabin A. B.: *Arch. Neurol. and Psychiat.*, 47, 938, 1942. (3.) Arkwright, J. A.: *Brit. Med. J.*, 2, 233, 1919.
- (4.) Baker, A. B.: *Journal-Lancet*, 63, 384, 1943. (5.) Biermond, A.: *Deutsch. Ztschr. f. Nervenhe.*, 143, 172, 1937. (6.) Bradford, J. R., Bashford, E. F., and Wilson, J. A.: *Quart. J. Med.*, 12, 88, 1918.
- (7.) Brown, M. R.: *Arch. Neurol. and Psychiat.*, 40, 800, 1938. (8.) Buzzard, E. F.: *Brain*, 3, 1, 1907.
- (9.) Casamajor, L.: *Arch. Neurol. and Psychiat.*, 2, 605, 1919. (10.) Casamajor, L., and Albert, G. R.: *Am. J. Dis. Child.*, 61, 99, 1941. (11.) Cobb, S., and Coggeshall, H. C.: *J. Am. Med. Assn.*, 103, 1608, 1934. (12.) Collens, W. S., and Rabinowitz, M. A.: *Arch. Int. Med.*, 41, 61, 1928.
- (13.) De Sanctis, A. G., and Green, M.: *J. Am. Med. Assn.*, 118, 1445, 1942.
- (14.) Fitzgerald, P. J., and Wood, A.: *U. S. Nav. Med. Bull.*, 43, 4, 1944. (15.) Ford, F. R., and Walsh, F. B.: *Bull. Johns Hopkins Hosp.*, 73, 391, 1943. (16.) Forster, F. M., Brown, M., and Merritt, H. H.: *New England J. Med.*, 225, 51, 1941. (17.) Fox, M. J., and O'Connor, R. D.: *Arch. Int. Med.*, 69, 58, 1942. (18.) Freitas Julião, O., and Couceiro, A.: *Rev. brasil de leprol. (num. espec.)*, 7, 97, 1939.
- (19.) Gardner, M., and Forbes, R. P.: *Rocky Mountain Med. J.*, 40, 394, 1943. (20.) Gareiso, A., Sageraras, P. D., and Mosquera, J. E.: *Arch. argent. de pediat.*, 17, 138, 1942. (21.) Garvey, P. H., Jones, N., and Warren, S. L.: *J. Am. Med. Assn.*, 115, 1955, 1940. (22.) Gayle, R. F., Jr., and Groom, D.: *J. Nerv. and Ment. Dis.*, 98, 488, 1943. (23.) Gilpin, S. F., Moersch, F. P., and Kernohan, J. W.: *Arch. Neurol. and Psychiat.*, 35, 937, 1936. (24.) Greenfield, J. G., and Carmichael, E. A.: *Brain*, 58, 483, 1935. (25.) Guillain, G.: *Arch. Neurol. and Psychiat.*, 36, 975, 1936. (26.) Guillain, G., Barré, J. A., and Strohl, A.: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 40, 1462, 1916.
- (27.) Hatoff, A.: *J. Pediat.*, 24, 393, 1944. (28.) Hecht, M. S.: *J. Pediat.*, 11, 743, 1937. (29.) Heernu, D.: *J. belge de neurol. et de psychiat.*, 39, 250, 1939. (30.) Hiller, R. I., and Fox, M. J.: *Marquette Med. Rev.*, 7, 152, 1943. (31.) Holmes, G.: *Brit. Med. J.*, 2, 37, 1917. (32.) Honeyman, W. M.: *Bull. Neurol. Inst. New York*, 6, 519, 1937.

- (33.) Jervis, G. A., and Strassburger, P. J.: *Am. J. Dis. Child.*, 65, 431, 1943. (34.) Jones, J. A., Holmes, J. W., and Weinstein, M.: *Am. J. Med. Sci.*, 206, 305, 1943.
- (35.) Kennedy, F.: *Arch. Neurol. and Psychiat.*, 2, 621, 1919.
- (36.) Landry, O.: *Gaz. hebdomadaire de médecine*, 6, 472, 486, 1859. (37.) Laurans, A.: *Paris Thésis*, No. 210, 1908. (38.) Lenègre, J., and Delair, G.: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 55, 712, 1939.
- (39.) Luque, O., and Pucheta Morcillo, R.: *Rev. méd. latino-am.*, 28, 473, 1943.
- (40.) McIntyre, H. D.: *Ohio State Med. J.*, 33, 875, 1937. (41.) Merritt, H. H., and Fremont-Smith, F. F.: *The Cerebrospinal Fluid*, Philadelphia, Saunders, 1938. (42.) Mills, C. K.: *J. Am. Med. Assn.*, 31, 11, 1898. (43.) Morris, M. H.: *Med. Rec.*, 156, 420, 1943.
- (44.) Osler, W.: *The Principles and Practice of Medicine*, New York, Appleton, 1892.
- (45.) Patrick, H. T.: *J. Nerv. and Ment. Dis.*, 44, 322, 1916. (46.) Pirzada, M. A.: *Indian Med. Gaz.*, 79, 298, 1944. (47.) Polan, G. G., and Baker, A. B.: *J. Nerv. and Ment. Dis.*, 96, 508, 1942.
- (48.) Roseman, E., and Aring, C. D.: *Medicine*, 20, 463, 1941. (49.) Rosenow, E. C.: *Arch. Int. Med.*, 64, 1197, 1939. (50.) Russell, W. O., and Moore, W. L.: *Arch. Neurol. and Psychiat.*, 49, 895, 1943.
- (51.) Sabin, A. B., and Aring, C. D.: *Am. J. Path.*, 17, 469, 1941. (52.) Sahs, A. L., and Paul, W. D.: *Arch. Phys. Ther.*, 24, 395, 1943. (53.) Shaskan, D.: *J. Nerv. and Ment. Dis.*, 97, 280, 1943. (54.) Spector, S.: *New York State J. Med.*, 42, 1959, 1942. (55.) Stearns, A. W., and Harris, H. I.: *U. S. Nav. Med. Bull.*, 43, 13, 1944. (56.) Stone, T., and Aldrich, K.: *J. Am. Med. Assn.*, 114, 2196, 1940.
- (57.) Susman, E., and Maddox, K.: *Med. J. Australia*, 1, 158, 1940.
- (58.) Toomey, J. A.: *J. Am. Med. Assn.*, 117, 269, 1941.
- (59.) Urquhart, D. A.: *Brit. Med. J.*, 2, 115, 1934.
- (60.) Viets, H. R.: *Arch. Neurol. and Psychiat.*, 17, 794, 1927. (61.) von Hagen, K. O.: *Los Angeles Neurol. Soc.*, 7, 198, 1942.
- (62.) Wickman, I.: *Acute Poliomyelitis*, Mono. 16, New York, Nervous and Mental Disease Publ. Co., 1913. (63.) Wolf, A.: *J. Nerv. and Ment. Dis.*, 92, 614, 1940.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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AND

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We regret that we have to omit the article regularly scheduled for this issue, as the Progress editor was unable to have a manuscript prepared for publication.

PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF NOVEMBER 20, 1945

The Effect of Injection Rate Upon the Anesthetic Dose, Lethal Dose, and Anesthetic Duration of Pentothal in Mice, and Strength-Duration Curves of Depression.

MILES H. ROBINSON, M.D. (Dept. of Pharmacology, Vanderbilt Univ.). Using a method of constant rate intravenous injection in mice whereby injection rates over a range of from about 6 to 600 mg./kg./min. was covered, it was found with pentothal that decreasing the injection rate raised both the AD50 and the LD50. Depending on what injection rates are used for these doses, the LD50/AD50 or therapeutic index of pentothal may lie between 3 and 10; and the modified index of Foster, $\left[\frac{LD1}{AD99} - 1 \right] \cdot 100$, which takes

into account the slopes of the dosage-effect curves, decreases to zero with sufficiently slow injection rates. Tentative evidence was secured that a given duration of anesthesia requires a fixed fraction of the margin between AD50 and LD50, regardless of the injection time. The factors of injection rate and injection duration were found to be related in a fairly regular manner for a given criterion of central nervous system depression, approximately according to the expression $y = Kx^{-\alpha}$, in which α varied from about 0.7 to 0.8. From such anesthetic and lethal curves of pentothal, and probably of most other hypnotics, LD50/AD50 can be estimated for any rate or time of injection common to both doses. These strength-duration curves of depression for the animal unit are similar to the strength-duration curves of excitation for the cellular unit, and reasons are given for the appropriateness of the analogy. An incidental finding was that mice raised on whole grains as compared to those raised on an elaborate ground-up pellet diet were found to have a progressively higher lethal

dose of pentothal as the injection rate is decreased, amounting to as much as a 50 % increase in the lethal dose.

The Analgesic Action of l-Amino-l-phthalidylpropane Hydrochloride. EDWIN J. FELLOWS, PH.D. (Dept. of Pharmacology, Temple Univ.). A new derivative, l-amino-l-phthalidylpropane hydrochloride ("phthalidyl") was appraised in animals from the standpoint of its possible effectiveness as an analgesic agent. These studies disclosed the following:

1. In rats (D'Amour-Smith method) "phthalidyl" elevated the threshold pain stimulus but aminopyrine did not. In cats (Eddy method) the latter induced only a slight elevation of the threshold pain stimulus, whereas "phthalidyl" exhibited marked activity. The acute toxicity of aminopyrine in rats was approximately 3 times greater than that of "phthalidyl."

2. In cats the effective dose range of "phthalidyl" was far in excess of that of demerol, codeine or morphine, although comparable elevation of pain thresholds was observed. "Phthalidyl" appeared to be almost entirely devoid of an excitatory component, whereas demerol, codeine and morphine produced effects which suggested a mixture of excitatory and depressant actions.

3. In experimental animals, the circulatory, gastro-intestinal, cardiac and respiratory actions of "phthalidyl" were found to be negligible. This suggests that its use as an analgesic agent would not be complicated by excessive side effects.

4. "Phthalidyl" evidenced activity when administered orally as well as parenterally.

CONCLUSION. Because of its marked threshold pain stimulus elevating action, low acute toxicity and relative lack of

side effects in animals, 1-amino-1-phthalidylpropane hydrochloride should receive clinical trial as an analgesic agent.

Artificial Respiration: A Comparison of the Schafer, Eve and Meltzer-Auer Methods in Two Apneic, Asphyctic Patients. JULIUS H. COMROE, JR., M.D., and ROBERT D. DRIPPS, M.D. (Dept. of Pharmacology and Harrison Dept. of Surgical Research, Univ. of Penna. School of Medicine and Dept. of Anesthesiology, Hosp. of the Univ. of Penna.). The Schafer prone pressure and the Eve gravity or tilting methods for artificial respiration have never before been compared quantitatively in typical cases of respiratory failure with asphyxia. We were able to compare various resuscitation techniques in 2 patients who had complete respiratory arrest for 2½ and 7 hours respectively. An endotracheal tube was passed through the larynx to ensure an open airway and respiration was measured by applying tightly a full face mask equipped with valves and conducting the expired air through a Bohr meter. The tidal air produced by the Schafer method varied from 71.5 to 117 cc., whereas that produced by the Eve gravity or tilting method varied from 286 to 500 cc. It is apparent that the Schafer method failed almost completely to ventilate these 2 unconscious, apneic and asphyctic patients. Reliance should not be placed on the Schafer method except as a very temporary emergency measure suitable only until more efficient methods can be instituted.

In these 2 patients, an attempt was made to sustain life by the Meltzer-Auer tracheal insufflation method. Oxygen was delivered through a catheter to the bifurcation of the trachea in each patient at a rate of 6 to 11 liters per minute. This resulted in initial arterial oxygen saturations of 95.8 and 90%. However, marked accumulation of CO₂ occurred with consequent acidosis. The CO₂ tensions in the arterial blood rose to 314 and 152 mm. Hg and the arterial pH fell to 6.67 and 6.86,

the latter being one of the lowest ever recorded in a living man. Artificial respiration therefore must not only oxygenate the blood but also eliminate excess CO₂; the latter apparently requires rhythmic chest movements.

Measurement of the Heat Exchange of the Foot. LOIS J. HOSBACH, E. S. MENDELSON and H. C. BAZETT, M.D. (Dept. of Physiology, Univ. of Penna.). A calorimeter is described into which the foot can be sealed and the heat output measured. The calorimeter is a double-walled copper vessel which is part of a closed system through which air is circulated. Non-evaporative heat loss can be calculated from the increase in temperature of the air passing through the calorimeter and the temperature difference across the walls. Evaporative heat loss is measured by absorbing the moisture present in the exit air. In use the calorimeter was suspended inside of a refrigerator box so that the environmental temperature of the foot could be regulated at a low level for the purpose of testing the insulating value of various cold weather footgear under conditions approximating those of actual use. Measurements of skin and boot surface temperatures were made simultaneously with determinations of heat loss.

The heat output of the foot was sometimes very low. An example is given in which the heat input into the foot can be calculated to be 21 kg. Cal/M²/hr. If it is assumed that the blood entered the foot at 36° C. and left at the temperature of the skin the blood flow could have been only about 0.1 ml./min./100 ml. tissue. It is suggested that a mechanism for heat economy exists in precooling the arterial blood. This work was done in close cooperation with Dr. Richard Day of the Climatic Research Laboratory who measured heat loss and blood flow. His work leads to a similar conclusion.

It is pointed out that the rate of cooling is not proportional to insulation if comparisons are made of clothing of varying heat capacities.

BOOK REVIEWS AND NOTICES

MEN, MIND AND POWER. By DAVID ABRAHAMSEN, M.D., Department of Psychiatry, Columbia University. Pp. 195. New York: Columbia University Press, 1945. Price, \$2.00.

THIS distinguished author proceeds to "direct attention to the psychologic forces behind the men instrumental in bringing about the most revolting drama the world has ever seen." He asks, and then answers the question, "What kinds of minds do these Nazis who instigated these atrocities have?" The treatise is discussed in the following chapters: The Riddle of the German Spirit; Why Germans Became Nazis; Men on the Scene; Quisling; Abnormal Messiah; Laval; The Man With the Janus Face; Remodelling the Minds of the Germans.

Brief personality sketches are given of the following Germans: Hitler, Goebbels, Goering, Himmler, von Papen, and Hess; also Quisling and Laval. Those Germans are described as maladjusted and as showing additional characteristics: With their insatiable lust for power, their strong emotions, they became engrossed in themselves and acquired a weak personality structure. Individually, they felt insecure and in reality they were rivals. They endeavored to function in the present, but their emotions were living in the past, and that was an old hatred of their immediate surroundings which they transplanted into their broader world.

The author has not meant to relieve Quisling of one iota of responsibility, nevertheless, in considering his disturbed mentality, he says: "He showed signs of mental conflict. Indeed his 'incendiary' speech was so filled with delusions that one gets the impression that he was actually a victim of those delusions for a short while. If we suppose that his condition was somewhat schizophrenic, we can say that Quisling probably barely escaped the disease." . . . "On a basis of his personality make-up, it seems probable that his mental derangement progressed." . . . "—all these make us consider Quisling as an abnormal Messiah." Viewed then, from such an angle, should not the "traitor" have been regarded as only

partly responsible? The Germans mentioned, are said to have been criminals before they were "war criminals." Though perhaps showing a bit of emotional bias, the treatise is very interesting and entertaining. N. Y.

THE CLINICAL APPLICATION OF THE RORSCHACH TEST. By RUTH BOCHNER, M.A., Psychologist, formerly Bellevue Psychiatric Hospital, and FLORENCE HALPREN, M.A., Psychologist, Bellevue Psychiatric Hospital, New York. Pp. 331. Second ed. New York: Grune & Stratton, 1945. Price, \$4.00.

IN this edition, the chapters on The Neurotic, The Schizophrenic and The Organic, are enlarged. Those on Intelligence, Behavior Problems and The Alcoholic, are added. The bibliography is more than trebled. There are the inclusions of a psychopathic personality study and an index, as was suggested previously by this Reviewer and it is his belief that since so much time is required for the complete Rorschach procedure, the inclusion of group studies—successfully employed elsewhere—would add to the popularity of the book. N. Y.

VIRUS AS ORGANISM. Evolutionary and Ecological Aspects of Some Human Virus Diseases. By FRANK M. BURNET, M.D., F.R.S., Director, Walter and Eliza Hall Institute of Research in Pathology and Medicine, Melbourne, Australia. Pp. 134. Cambridge, Mass.: Harvard Univ. Press, 1945. Price, \$2.00.

DR. BURNET's excellent monograph was prepared for the Harvard University Edward K. Dunham Lectures for the Promotion of the Medical Sciences. The manner of treatment is well indicated in the title and subtitle. Viruses are treated from the biologic point of view as organisms under the fundamental necessity of survival in the parasitic state, and viral diseases are shown to represent the dynamic interrelationships between host and parasite, whose long term trend is toward mutual tolerance; this, of course, is a point of view very cogently developed earlier by Theobald

Smith in regard to higher parasitic organisms. In lectures such as these Dr. Burnet in his own words was able "to indulge in speculation about origins and change in virus disease beyond what would be admissible in general scientific writing." The speculations are illuminating and valuable because of the author's wide acquaintance with general biology and his very intensive laboratory experience with viral diseases. Herpes, poliomyelitis, psittacosis and related infections, smallpox, alastrim and vaccinia, yellow fever and influenza in each case receive a chapter. The serious student of virus diseases will derive both pleasure and benefit from Dr. Burnet's treatise.

S. M.

MANUAL OF PSYCHOLOGICAL MEDICINE. For Practitioners and Students. By A. F. TREDGOLD, M.D., F.R.C.P., F.R.S.E., Consulting Physician in University College Hospital, London. Pp. 308; 2 tables. Second ed. Baltimore: Williams & Wilkins, 1945. Price, \$5.00.

PSYCHOLOGIC medicine is described as "that branch of medicine which is concerned with disease of mind apart from body." In less than 9 months, the first edition of this work was out of print. In the classification of Mental Disorders, Decay and Defect, the list given is long. The subject matter is discussed in 27 chapters, and in this review some of the more important ones are grouped for space economy: The Normal Mind; General Symptomatology, Anxiety States, Neurasthenia and Epilepsy; the Manic-Depressive, Schizophrenic, Paraphrenia and Paranoia Psychoses; Mental Disorders Due to Toxins, Infections, Syphilis of the Brain, Head Injury, and Those Associated With Child-Bearing, Mental Defect and Moral Defect.

The chief additional matter given is: "Pitressin in the diagnosis of epilepsy; cerebral malaria; mental disorder due to vitamin deficiency; mental disorder due to Parkinsonism; prefrontal leukotomy; alterations in the law in regard to divorce in insanity and infanticide."

Since most subjects with the much discussed psychopathic personality do not become interned in mental hospitals or jails, and since the general practitioner must come in contact with them fairly often, some

comprehensive consideration of these disturbers would prove helpful. The great economic and other advantages of foster homes for selected mental and defective subjects is worthy of inclusion. Under Legal Relationships, the descriptions of the care and control of mental disorders and defects, civil relationships and criminal responsibility are those employed in England, and necessarily not wholly applicable here. Otherwise the subject matter is well adapted to the needs of our general practitioners and students. N. Y.

BACK TO LIFE. The Emotional Adjustment of Our Veterans. By HERBERT I. KUPPER, M.D., Staff Psychiatrist, U. S. Marine Hospital, Ellis Island, N. Y. With a Foreword by DR. ROBERT H. FELIX, Chief, Mental Hygiene Division, U. S. Public Health Service. Pp. 220. New York: L. B. Fischer, 1945. Price, \$2.50.

THIS military psychiatrist is well qualified to discuss the perplexing problems of readjusting the fighting wartime emotions of the veterans to peacetime needs, also of readjusting the community. The returning service man is spoken of as less adequate and less secure than before his induction. "He will certainly describe the world around him as less friendly, ungrateful, and vicious . . ." The subject matter is presented in the following chapters: Every Man Is Supposed to Have His Place in the World—But Where Is Mine?; The Fighting Man; Home Again; Native Land; Back to Life. Brief case histories show some of the difficulties and give appropriate measures for overcoming them. Unexpected manifestations may appear: While some artists and writers show impaired ability, others may have greater skill. Following sexual deprivation, for a time there may be psychic impotence; or the veteran may become promiscuous, but little homosexuality is experienced unless the vice was practiced before induction. Instead of quiet following sedation, a sudden release of pent-up memories may result in violence.

The rules of the National Committee of Mental Hygiene are included, some of which are: Love him and welcome him. Listen well. Face the reality of the disability; don't try to ignore it, but don't magnify it; focus on what is left, not what is lost.

Treat him as an essentially normal, upstanding, competent person, not as an invalid. Commend his efforts and successes and ignore the slips. Expect him to be different in some ways. Take time to get acquainted again and to find ways of getting along together. Allow him time and freedom in getting acquainted with the old places and in reestablishing his old contacts. Create an atmosphere of expectancy: encourage him to take up his favorite hobby or sport, to return to work as soon as he is able, and to lead a normal social life; but avoid pushing or regulating him. Get professional help if it is needed. Don't just muddle through. Let your own faith and beauty of spirit be your chief stock-in-trade. N. Y.

NEW BOOKS

Human Embryology (Prenatal Development of Form and Function). By W. J. HAMILTON, M.D., D.Sc., F.R.S.E., Professor of Anatomy in the University of London at the Medical College of St. Bartholomew's Hospital; and J. D. BOYD, M.A., M.Sc., M.D., former Fellow of Clare College, Cambridge; Professor of Anatomy in the University of London at the Medical College of the London Hospital. Pp. 366. Baltimore: Williams & Wilkins, 1945. Price, \$7.00.

Back to Life. The Emotional Adjustment of Our Veterans. By HERBERT I. KUPPER, M.D., Staff Psychiatrist, U. S. Marine Hospital, Ellis Island, N. Y. With a Foreword by DR. ROBERT H. FELIX, Chief, Mental Hygiene Division, U. S. Public Health Service. Pp. 220. New York: Fischer, 1945. Price, \$2.50.

Physical Chemistry of Cells and Tissues. By RUDOLF HOBBER, University of Pennsylvania School of Medicine, Philadelphia. Pp. 676; 70 ills. Phila.: Blakiston, 1945. Price, \$9.00.

Cleft Palate and Speech. By MURIEL E. MORLEY, B.Sc., F.C.S.T., Speech Therapist to the Royal Victoria Infirmary, The Hospital for Sick Children, and The Newcastle General Hospital, Newcastle-upon-Tyne. Pp. 156. Baltimore: Williams & Wilkins, 1945. Price, \$2.75.

The Medical Clinics of North America. Symposium on Gynecology and Obstetrics. Philadelphia Number. Phila.: Saunders, 1945. Price, \$16 per year.

Vitamins and Hormones. Vol. III. Edited by ROBERT S. HARRIS, Assoc. Professor of Nutritional Biochemistry, Massachusetts Institute of Technology, Cambridge, Mass., and KENNETH Y. THIMANN, Assoc. Professor of Plant Physiology, Harvard University, Cambridge, Mass. Pp. 420; numerous figs. and tables. New York: Academic Press, 1945.

Hematology. For Students and Practitioners. By WILLIS M. FOWLER, A.B., M.D., Professor of Internal Medicine, University of Iowa, Iowa City. With a Chapter by ELMER L. DEGOWIN, A.B., M.D., Assistant Professor of Internal Medicine, University of Iowa. Pp. 499; 110 figs. New York: Hoeber, 1945. Price, \$8.00.

The Bacterial Cell. In Its Relation to Problems of Virulence, Immunity and Chemotherapy. By RENE J. DUBOS, George Fabyan Professor of Comparative Pathology and Professor of Tropical Medicine, Schools of Medicine and Public Health, Harvard University, Member of the Rockefeller Institute. With an Addendum by C. F. ROBINOW, Strangeways Laboratory, Cambridge, England. Pp. 460. Cambridge, Mass.: Harvard Univ. Press, 1945. Price, \$5.00.

The Extremities. By DANIEL P. QUIRING, Ph.D., Head of the Anatomy Division, Cleveland Clinic Foundation, and Assoc. Professor of Biology, Western Reserve University. Pp. 117; 106 engravings. Phila.: Lea & Febiger, 1945. Price, \$2.75.

Dr. W. C. Röntgen. By OTTG GLASSER, Cleveland Clinic Foundation. Pp. 169. Springfield, Ill. Charles C Thomas, 1945. Price, \$4.50.

NEW EDITIONS

The Clinical Application of the Rorschach Test. By RUTH BOCHNER, M.A., Psychologist formerly Bellevue Psychiatric Hospital, and FLORENCE HALPERN, M.A., Psychologist, Bellevue Psychiatric Hospital, New York. Second ed. Pp. 331. New York: Grune & Stratton, 1945. Price, \$4.00.

Prescribing Occupational Therapy. By WILLIAM RUSH DUNTON, JR., M.D. Second ed. Pp. 151. Springfield, Ill.: Thomas, 1945. Price, \$2.50.

Modern Urology for Nurses. By SHEILA MAUREEN DWYER, R.N., B.S., Director, School of Nursing and Nursing Service, Southampton Hospital, Southampton, N. Y., and GEORGE W. FISH, M.D., Associate Professor of Urology, College of Physicians and Surgeons, Columbia University, New York City. Second ed. Pp. 287; 66 engr. Phila.: Lea & Febiger, 1945. Price, \$3.25.

The Physician's Business. Practical and Economic Aspects of Medicine. By GEORGE D. WOLF, M.D., Assistant Clinical Professor of Otolaryngology, New

York Medical College, New York; Fellow, New York Academy of Medicine. Foreword by HAROLD RYPINS, A.B., M.D., F.A.C.P. Second ed. Pp. 433; 58 ills. Phila.: Lippincott, 1945. Price, \$6.00.

This book aims to show how to "systematize work to be done, and how to institute many tested time and money-saving ideas.

"The author tells what fees to charge, how to collect bills, how to institute simple accounting procedures, ways to cut insurance costs, etc." The author gives many details on office economics and answers regarding business methods and business ethics.

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WITH this number, THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES changes its size for the first time in its existence of 125 years. The reasons for this are twofold. Of chief concern to the reader is that the greater width of the printed page permits the use of double columns, which expert investigations have shown to be easier than a single column on the eye and attention of the reader. Secondly, a number of medical advertisers have agreed among themselves to furnish cuts in 3 sizes only, so that our longer, wider page will conform to their medium size cut. We regret the passing of the journal's distinctive size, but hope that its equally distinctive yellow cover will long be maintained. It may be of interest to note here that when the supply of yellow cover papers was recently exhausted and could not be renewed, it was found desirable to preserve the familiar "Yellow Journal" by printing white paper in yellow, though this required two passages through the press.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

FEBRUARY, 1946

ORIGINAL ARTICLES

MENINGOCOCCUS MYOCARDITIS

REPORT OF TWO CASES WITH ANATOMICAL AND CLINICAL CHARACTERISTICS

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IN his excellent review of myocarditis in 1941, Saphir⁷ emphasizes the large number of diseases in which inflammatory lesions of the myocardium are encountered by the pathologist, in contrast to the relative rarity with which antemortem diagnosis is established.

Today myocarditis is an unpopular diagnosis because of its ungarded employment by an earlier generation who sought an anatomical explanation for all evidences of altered physiology to which the heart is spectacularly liable. Speaking of this abuse of diagnostic criteria, Sir Thomas Lewis⁴ states that in his opinion the clinical recognition of myocarditis can hardly be established except in rheumatism, and that in such instance he favors using the more inclusive term, "carditis" because pericardium and endocardium are rarely untouched when the myocardium is involved.

By inference it became accepted practice to diagnose rheumatic myocarditis when the more readily recognizable clinical signs of endocardial or pericardial disease were present. When the electrocardiographic criteria of acute rheumatic myocarditis were described,¹ early and accurate

diagnosis was materially advanced, especially when it became possible to differentiate acute pericarditis⁹ with some degree of surety.

Gradually the worth of similar electrocardiographic criteria has been recognized in the study of myocarditis in diseases other than rheumatic fever. Published reports suggest that acute myocarditis is not an uncommon complication of acute systemic infection, and rheumatic fever is no longer considered unique in this respect. In the growing list, meningococcus infection is a notable omission.

Saphir⁸ states that in his opinion meningococcus myocarditis is common in cases who succumb to the infection. If this is true, the diagnosis is as commonly missed by physician as by pathologist. Hartwell² reported on a case of myocarditis with postmortem findings and at that time was able to find 12 other such cases in the literature. A recovered case of meningococcemia with myocarditis proved by electrocardiography has been recently reported.⁵ It has occurred to us that cases suffering from acute myocarditis due to meningococcus may sometimes be confused with the currently popular hypo-

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VOL. 211, NO. 2—FEBRUARY, 1946

adrenal syndrome (Waterhouse-Friederichsen), and that the differentiation is of utmost importance. Meningococcus infections are prevalent during the present war, but effective new therapeutic agents have reduced the mortality, thus opening a new field involving the medical care of those cases which recover. It is therefore, with a view to better understanding and treatment of such survivors, that 2 cases are being reported in some detail.

Case Reports. CASE 1. A white male, 23 years of age, was admitted to hospital complaining of sore throat, cough and headache of 36 hours duration. Physical examination revealed inflammation of the nasopharynx, enlarged tonsils, a few moist râles at the base of the right lung, and an appearance of toxicity out of proportion to these findings and a fever of 99.8° F. (M).

Although the skin was normal on admission, multiple, small, purpuric lesions developed within 3 hours. The temperature rose, tachycardia appeared, headache increased, and definite nuchal resistance became apparent. The spinal fluid contained 1900 white cells per c.mm. and meningococci were cultured from it. The organisms were also grown from the blood at this time. The total white blood cell count was within normal limits but rose to 41,000 the day after admission.

Sulfadiazine was immediately commenced when the diagnosis of meningococcic septicemia and meningitis became apparent, 3 hours after admission. The patient was given 5 gm. intravenously and 12 gm. orally during the first 24 hours, following which the concentration of blood sulfadiazine had reached 23.7 mg. per 100 cc. Sulfadiazine was omitted for the next 3 days because of renal failure associated with circulatory collapse to be described below. The sulfa concentration in the blood did not fall perceptibly until circulatory improvement, evident on the 5th hospital day. Sulfadiazine was again given and continued in gradually decreasing doses for 3 weeks, or until the 23rd day of the patient's illness. The blood sulfa level was maintained between 13 and 23.7 mg. % (daily determinations) between the 3rd and 10th day of illness, and consistently below 13 mg. %, thereafter. A total dosage of approximately 125 gm. of sulfadiazine was given.

A minimum urinary output volume of 1500 cc. per 24 hours was maintained except during the period of oliguria mentioned. While he was conscious and able to swallow, sufficient sodium bicarbonate was given to alkalinize the urine.

Despite immediate chemotherapy the patient had a stormy course. The neck rigidity increased, he became semiconscious and developed bowel and urinary incontinence. The purpura increased and coalesced until no part of the body was free of lesions, superficially, except for the left fifth toe which developed gangrene of its tip. There were severe bilateral subconjunctival ecchymoses and large herpetic bullæ on the lips.

After admission the patient went into circulatory collapse. Blood pressure fell from 100/60 to 80/40. The pulse rate was rapid and of poor quality; respirations were rapid and shallow; he vomited and there was well marked dependent edema, especially about the ankles. It was difficult to distinguish the extravasations of blood from edema, especially around the eyelids. Blood non-protein nitrogen had increased to 66 mg. %. This phase (circulatory collapse) was treated successfully by routine anti-shock measures including blood plasma. Adrenal failure was hypothesized and cortical extract would have been added to the therapy, had it been available. It was several days before normal renal function reappeared, the interval being characterized by low blood pressure, oliguria, peripheral edema, elevation of N.P.N., and slow excretion of sulfadiazine.

The neck became flaccid late on the 3rd day of illness but fever continued and convalescence was slow. The fever reached approximately 102° F. (R) daily for 10 days and 100° F. for 14 additional days. Severe headaches were recurrent. He lost a total of 25 pounds in weight and was troubled by numerous ulcers from necrosis of the larger purpuric lesions.

The prolonged fever was reason for continuous concern. In retrospect, it seems unlikely that the meningococcus organisms were viable throughout. It seems more probable that the secondary effects of infection, *i. e.*, tissue destruction, extravasation of blood into the tissues, toxicity and general debility, were responsible.

The heart did not attract attention except during the period of low blood pressure and

circulatory collapse when the rate was rapid and the sounds were of poor quality with occasional irregularity of rhythm. After the 5th day of illness, nothing untoward was noted and electrocardiograms were taken. On the 28th day he was allowed up gradually about the ward. This he seemed to tolerate very well, but activities were necessarily limited by reason of the gangrenous toe, described above.

On the 33rd day of illness he complained of slight nausea and of his heart "skipping beats." He was put to bed, the pulse became regular, and nausea was relieved. He slept well that night. The following morning (0630 hours), he had what the ward attendant described as a "convulsion." The nurse found him cyanotic, "pulseless and dyspneic." Resuscitation was unsuccessful and the patient was pronounced dead at 0650 hours.

Necropsy (by Capt. R. A. Kritzler, M.C.). Army Medical Museum Acc. No. 111870.

Exterior: There were brown purpuric areas in the skin that measured from 0.5 to 0.8 cm. across.

Pleural cavities: Both were obliterated by fibrous adhesions.

Heart: Weight 310 gm. The right atrium and ventricle were slightly dilated. The epicardium, endocardium and heart valves were normal. The outer 0.2 to 0.3 cm. of the myocardium over all chambers and the septum was a light brown color, glistening and soft in striking contrast to the light red underlying muscle.

Lungs, spleen, liver and kidneys were normal.

Suprarenals: The left was somewhat smaller than normal but otherwise there was no evident gross abnormality.

Gastro-intestinal tract: There were small petechial hemorrhages in the rugae of the gastric mucosa.

Brain: Weight 1270 gm. There were small opaque areas in the leptomeninges over both cerebral hemispheres.

Microscopic examination: The section through the outer part of the left ventricle is illustrated in Figure 1. The epicardium, subpericardial adipose tissue and branches of the coronary arteries are normal. A sharply demarcated outer zone comprising nearly one-third of the myocardium, is virtually devoid of muscle fibers, the stroma is collapsed and the small capillaries lie close

together. There is infiltration with a few lymphocytes and monocytes, many of the latter containing phagocytized yellow amorphous pigment. Scattered within this area are a few faintly stained swollen and vacuolated muscle fibers. This is most conspicuous at the junction of normal and degenerated tissue (Fig. 2). In none of these areas is there proliferation of fibrous tissue.

In the myocardium are small widely disseminated areas of edema, capillary engorgement and degeneration characterized by loss of, or pyknosis, of nuclei, and swelling or complete absence of muscle cells (Fig. 3). In some places only bundles of myofibrils remain. Evidence of inflammation is conspicuously absent and the intramural arteries and arterioles are normal. The muscle fibers near the endocardium are pale and swollen, but for the most part the striations remain. A section through the interventricular septum is similar and the alteration is most marked in the subendocardial fibers. Adjacent to the conduction bundle is an elongated mass of fused, swollen, pale staining muscle cells, elsewhere are large focal occasionally perivascular areas of degeneration.

A section through the right ventricle was similar, but the degeneration was more patchy.

Suprarenal: In both the reticular and fascicular zones, partial or complete loss of cortical cells, collapse of the reticular network and dilation of the sinusoids is noted (Fig. 4). Large numbers of phagocytes are filled with iron-containing pigment.

CASE 2. A white male, 24 years of age, was admitted to hospital approximately 36 hours after the sudden onset of chills, fever, headache, and pains in knees and elbows. On admission he was stuporous; his temperature was 104.2° F., pulse 120, and respiration 28 per minute. He had an extensive fine purpuric rash over the skin, and ecchymoses of the mucous membranes of the soft and hard palate, and subconjunctivae of both eyes. There was definite stiffness of the neck. The spinal fluid contained 412 white cells per c.mm. and gram-negative diplococci were seen in the direct smear, but did not grow in culture. Meningococci were grown from the blood culture. The leukocyte count was 16,600.

Sulfadiazine was started at once, both intravenously (5 gm.) and by mouth. On the following day (3rd of illness) the blood

level was 10.5 mg. %. Thereafter reasonably good concentrations were maintained with difficulty on adequate dosage. During the subsequent 9 days the average level was 8 mg. %, with a maximum of 12.7 and minimum of 2.5 mg. %.

During the first 24 hours in hospital the patient was very ill and an early Waterhouse-Friederichsen syndrome was then suspected. Hourly blood pressure readings were taken. The lowest recorded was 87/45. With it circulation was fully maintained.

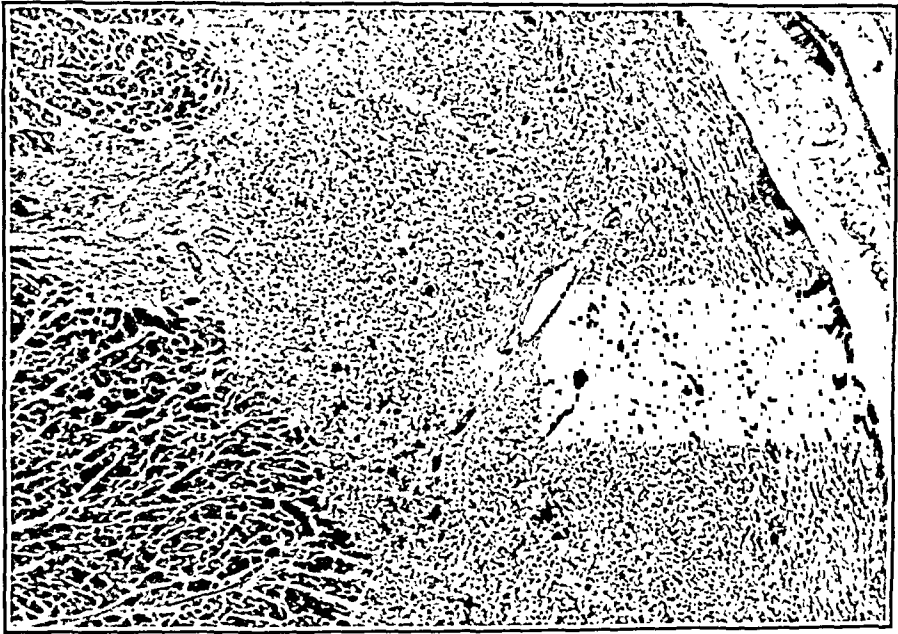


FIG. 1.—A section through the pericardial surface of the left ventricle. Practically all the muscle fibers have disappeared and an area of degeneration is infiltrated with lymphocytes and monocytes. $\times 50$. (U. S. Army Medical Museum Neg. No. 82567.)

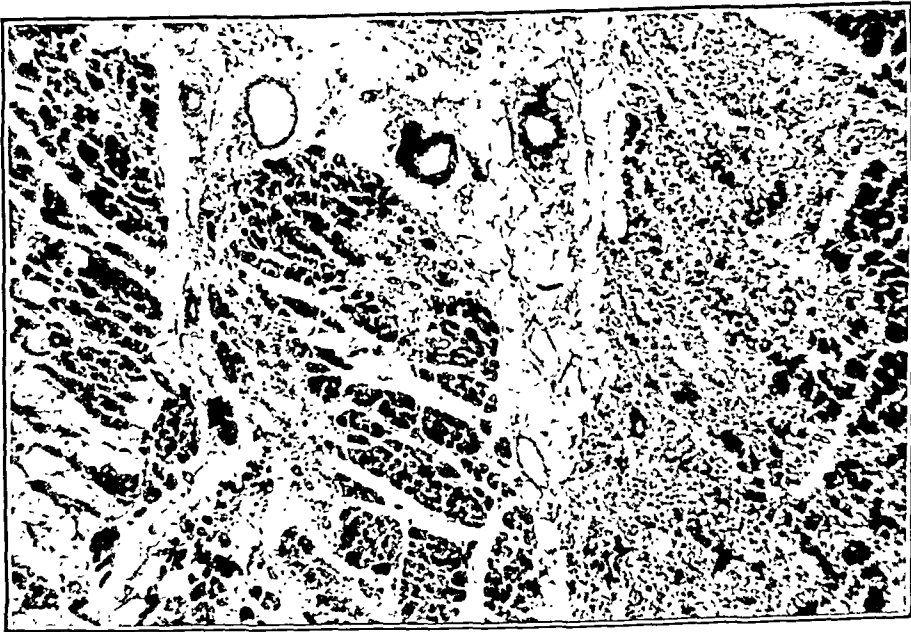


FIG. 2.—A section from the margin of an area of degeneration. $\times 120$. (U. S. Army Medical Museum Neg. No. 82570.)

On the 3rd day of illness he commenced to improve, rapidly became oriented, and all signs of meningeal irritation disappeared.

On the 4th day, the heart sounds were of poor quality, and largely because of experience with Case 1, an electrocardiogram was taken (Fig. 5).

The purpuric rash reached its peak on the 5th day of illness and from then onward an occasional new lesion was noted but the rash as a whole faded as he continued to improve.

On the 8th day he complained of pains in both wrists which were slightly swollen. The next day, the left elbow and left knee

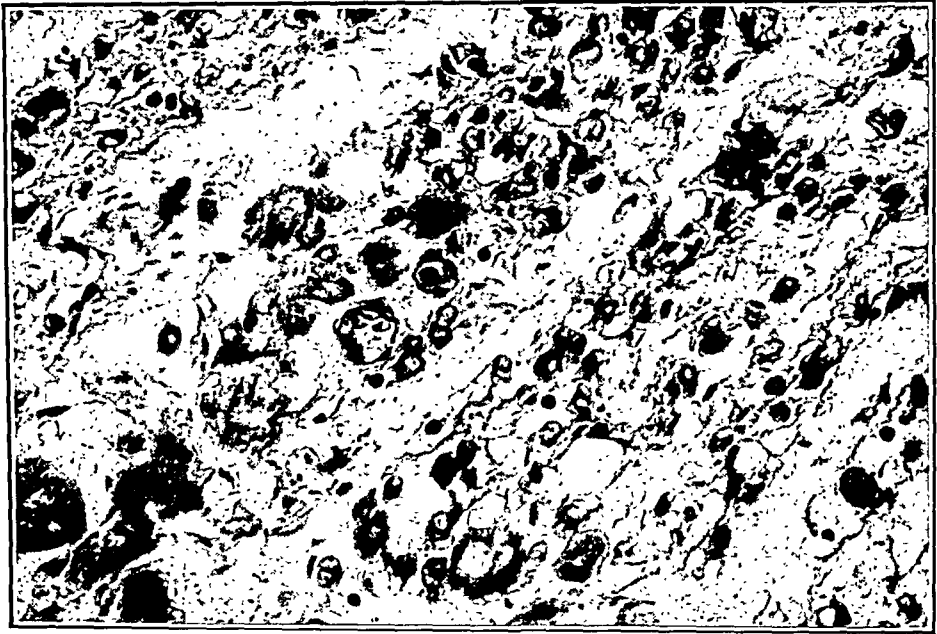


FIG. 3.—A higher magnification to show muscle degeneration. $\times 705$. (U. S. Army Medical Museum Neg. No. 82564.)

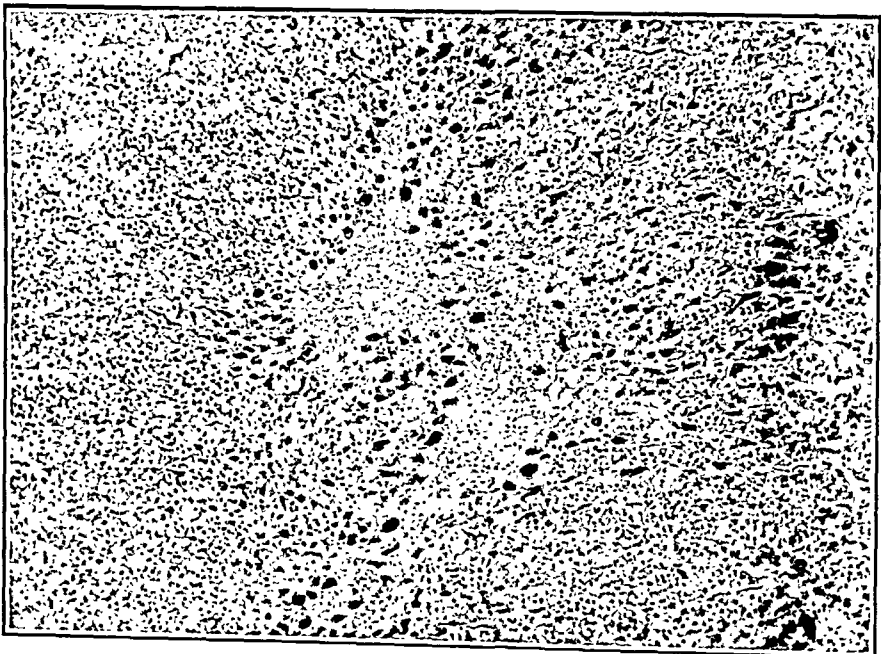


FIG. 4.—A section of suprarrenal to illustrate degeneration of cortical cells and dilatation of sinusoids. $\times 700$. (U. S. Army Medical Museum Neg. No. 83213.)

were worse, and he had sharp pains in both eyeballs. The retinal fundi were normal and the media clear. By the 11th day, the left elbow was considerably swollen, the white blood count which had subsided returned to 15,000 per c.mm., and there was low-grade fever. Sulfadiazine was discontinued at this time because the patient was no longer responding favorably to it.

He was treated symptomatically and

observed for the ensuing 36 hours. The temperature rose to 101° F. and he developed a heavy fresh maculopapular, salmon-colored rash frequently associated with chronic low-grade meningococcemia. There was no recurrence of purpuric phenomena. The left elbow was aspirated, but only a few drops of clear sterile fluid was obtained. A blood culture was also reported sterile.

Clearly meningococcemia was still present,

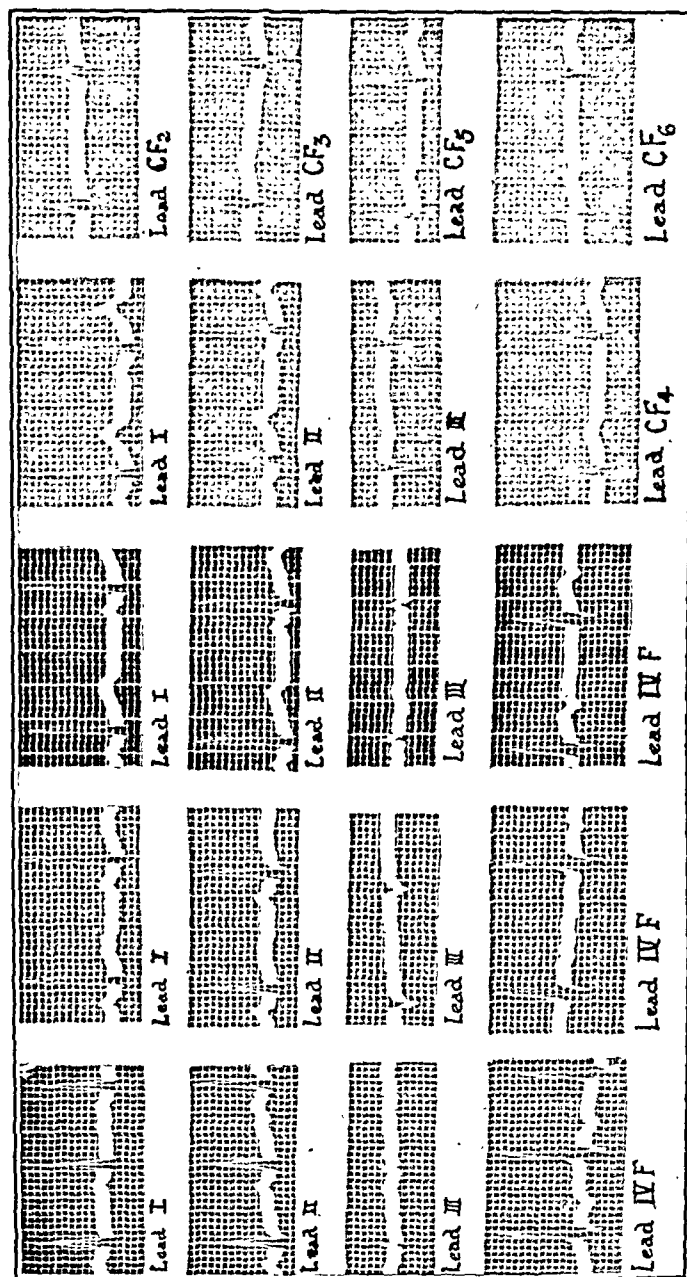


FIG. 5.—Selected serial electrocardiograms, Case 2, taken during course of acute meningococcemia. A, June 18, 1944—4th day of illness. Sinus tachycardia, rate 124 per min. P-R, 0.16 sec. QRS, 0.08 sec. Note the isoelectric T waves, Lead I, diphasic Leads II and III, and negative Lead IV F. B, June 21, 1944—7th day of illness. Sinus rhythm, rate 88 per minute. P-R, 0.16 sec. QRS, 0.08 sec. Note that the T waves are now positive in Lead I (notched) and Lead II; diphasic Lead IV F. C, June 25, 1944—11th day of illness. Sinus rhythm, rate 70 per min. P-R, 0.16 sec. QRS, 0.08 sec. Note further improvements in T waves. D, August 22, 1944—69th day of illness. Sinus rhythm, rate 86 per min. P-R, 0.16 sec. QRS, 0.08 sec. The additional precordial leads are included. Note the well-formed T waves in all leads with the exception of CF₆. Earlier records of Lead CF₆, the T waves had been negative. The T waves in Lead III have become negative.

but no longer fulminating. It seemed probable that this was an *in vivo* exhibition of meningococcus-acquired sulfonamide resistance,³ in this instance contributed to by a lower blood concentration than optimum during a 9 day course of sulfadiazine. There were in addition, signs of moderate sulfonamide lithiasis so the therapy was changed. Penicillin injections (25,000 units every 2 hours, intramuscularly) were given with immediate and permanent cure of infection. A total of 650,000 units of penicillin was used.

The cardiac sounds progressively regained strength and tone after the 4th day of illness. On the 8th day a soft blowing systolic murmur appeared at the pulmonary area and apex. It persisted and had the characteristics of a functional pulmonic murmur. On the 23rd day of illness the patient became aware of "skipping" of the heart. He was at bed rest and under no unusual stress. No arrhythmia was found. Frequent electrocardiograms taken during the patient's stay in hospital showed acute type serial changes in the terminal segments of the ventricular complexes. Selections from these tracings are reproduced in Figure 5. The cardiac silhouette was normal on each of several roentgenologic examinations.

Physical activity was restrained long after the patient had symptomatically recovered, chiefly because the electrocardiographic pattern was slow to stabilize and the erythrocyte sedimentation rate continued to be slightly elevated. He was allowed up gradually on the 61st day of illness, and from thence onward had an uneventful convalescence. When last heard from, 5 months after onset of his illness, he was being sent to full duty. A recent electrocardiogram is said to be normal but is not available for comparison with our series.

Discussion. Acute myocarditis occurs in meningococcus infection, although only a small number of cases are recorded.^{2,5,8} It is sometimes associated with endocarditis, but the type under consideration occurred without involvement of endocardium and pericardium.

Saphir^{7,8} describes the histology of meningococcus myocarditis as: (1) hemorrhagic exudation, (2) early appearance of endothelial leukocytes, (3) destruction of muscle fibers, and (4) presence of intra-

cellular Gram-negative diplococci. It is important that all his cases died during an active phase of infection. This accounts for the presence of organisms in the muscle, and also indicates the severity of the infection in which acute myocarditis is known to have developed.

Toxemia and severe systemic infection were clinical features in both of our cases, and as pointed out, have likewise been conspicuous in recorded cases. Damage to the heart fibers adjacent to the conduction bundle is worthy of note since it seems fair to assume that it may have contributed directly to the unexpected death of this soldier. Saphir⁸ noted a similar location of damage in some of his cases and speculated upon its importance.

Because of the high blood concentration and the unusually long duration of sulfadiazine therapy in Case 1, the possible toxic effects of the drug on heart muscle must be considered. However, no lesions suggestive of drug damage were found in other viscera, and sulfonamides tend to cause a diffuse myocarditis rather than localized degeneration. Also myocarditis occurred in meningococcus infections prior to the discovery of sulfonamides; in our second case, it occurred with relatively low blood sulfa concentrations.

To obtain information on the incidence, of meningococcus myocarditis, electrocardiograms were taken on a series of 8 cases. One or more tracings were taken between the third and fifth days, the period when changes were noted in Case 2, and compared with a control taken after full recovery. Several of the cases had severe epidemic meningitis, two were comatose, but none exhibited signs of fulminating septicemia. No electrocardiogram deviated significantly from normal. Since one of the distinguishing signs of fulminating septicemia is severe toxemia and acute myocarditis occurs most frequently in such cases, it seems probable that meningococcus toxin may be of importance.

As regards the incidence of meningococcus myocarditis, the supposition that it occurs chiefly in cases of fulminating

septicemia automatically imposes limitations since these cases are rare when compared with the total number infected. Within the group liable to the complication clinical experience (D. V. H.) leads us to suspect it may be relatively high, since these are the only 2 cases of fulminating septicemia seen during 2 years in a large hospital installation in the European Theater of Operations, where meningococcus infections were continuously encountered. On review of 29 autopsies on cases of meningococcus infection studied in this theater a lower incidence was found (D. M. A.). The heart was recognized as the cause of death in only 1 individual (Case 1) when no more than routine examination of the heart (gross and microscopic) had been made. Nevertheless 7 of 29 showed some noteworthy degree of acute myocarditis. Seventeen of the group died with fulminating septicemia, and 12 predominantly with meningitis. Six of the 7 cases with myocarditis occurred in association with septicemia whereas only a single case appeared among the remaining 12. This was similar to Saphir's observation of a 20% incidence in a group of 10 autopsies. It is clear that further observations, anatomical as well as clinical, are necessary to assess the expected incidence of meningococcus myocarditis but on the basis of known facts, it is apparent that it occurs more often than is generally appreciated.

The phenomenon of circulatory collapse, or shock (Waterhouse-Friederichsen syndrome), is a well recognized entity which occurs in cases of fulminating septicemia. It is popularly supposed to be directly caused by adrenal failure, because the cases resemble Addisonian crises and because both adrenal glands are often destroyed by hemorrhage. The explanation is not entirely satisfactory. Onset of the syndrome in humans is usually rapid, often within a few hours of onset of illness, while laboratory animals with bilateral cortical extirpation develop symptoms after 48 or more hours, and Rogoff and Stewart⁶ report 7 days average survival

of dogs after adrenalectomy. Whereas small fragments of cortical tissue are sufficient to maintain life in animals, collapse and death in humans are observed without corollary evidence of gland injury. The depression of blood pressure, urinary suppression, hemoconcentration, and elevation of nitrogenous waste in the blood, are common in so-called surgical shock, and not necessarily dependent upon reactions of either adrenal glands or liver. The adrenal histology in our case suggests unilateral damage which probably occurred during the acute infectious phase, but whether or not it was functionally significant, we are unable to determine. It is probable that the myocardial damage may have contributed more than the adrenal damage, and that the observed fall in blood pressure could have been wholly explained by reduction of cardiac output.

Although it is well known that acute heart failure may be indistinguishable from peripheral vascular failure the recognition of myocarditis is of great importance for the selection of proper therapy. Differentiation would be of negligible practical importance were it not for the fact that indications for treatment are different. Measures taken to increase circulating blood volume in the one, may prove fatal in the other. Case 1 responded to therapeutic trial as one would expect in peripheral vascular failure, which has some weight as regards the mechanism in that individual case. On the other hand the coexisting myocardial damage was an unsuspected element, and it was fortunate the therapeutic procedures undertaken were within the functional capacity of the damaged organ.

Convalescent care in meningococcus myocarditis is the other important consideration. The primary objective of convalescence is the repair of the damaged tissues and intelligent planning presupposes full recognition of the extent of this damage. In Case 2 treatment was planned to reduce cardiac work to a minimum, over a sufficiently long period to allow

healing. The optimum time for bed rest needs to be determined on a larger series of cases, but on the basis of these 2 cases a minimum of 6 weeks is believed desirable. This period is suggestively similar to the average duration of myomalacia following myocardial infarction. Hyperirritability of the heart as indicated by awareness of cardiac irregularity in both cases merits special consideration, and may occur as late as the fifth week of illness. The common prophylactic measures, including quinidine, should be employed.

Summary and Conclusions. 1. Two cases of meningococcus myocarditis are presented. Both had fulminating septicemia, one with definite signs of circulatory collapse (Waterhouse-Friederichsen syndrome), the other without.

2. The diagnosis of acute myocarditis was proven in 1 case by anatomic examination following a cardiac type death on the 33rd day of illness. The soldier had been treated with sulfadiazine for his infection, which was cured, and had survived early circulatory collapse as well.

3. The diagnosis of acute myocarditis was suspected in the second case because of clinical observation and experience with Case 1. An electrocardiogram on the fourth day of illness showed important changes. The serial electrocardiograms are reproduced and other findings associated with convalescence described.

4. It is believed that the myocardial damage was not a result of sulfonamide toxicity.

5. Clinical recognition of acute myocarditis will be facilitated when its association with fulminating meningococcemia, is appreciated. Diagnosis is critically important early in the disease when signs of circulatory collapse supervene in planning convalescence.

6. A tendency to cardiac arrhythmia occurring as late as the fifth week of illness should be kept in mind and prophylactic precautions should be undertaken when there is evidence of hyperirritability of the heart.

The interest and inspiration of Col. William S. Middleton, M.C., A.U.S., in preparation of this manuscript is gratefully acknowledged.

REFERENCES

1. COHN, A. E.: Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, *J. Exp. Med.*, **39**, 1, 1924.
2. HARTWELL, R. M.: Meningococcic Endocarditis and Myocarditis, *Am. J. Dis. Child.*, **58**, 823, 1939.
3. HENRY, R. J.: The Mode of Action of Sulfonamides, *Rev. Ser.*, Josiah Macy, Jr., Foundation, Vol. II, No. 1, 1944.
4. LEWIS, SIR T.: *Diseases of the Heart*, New York, Macmillan, 1934.
5. RAPPAPORT, J. N., and ZUCKERBROD, M.: Recovery from Fulminating Meningococcic Infection with Myocarditis Proved by Electrocardiography, *J. Lab. and Clin. Med.*, **30**, 307, 1945.
6. ROGOFF, J. M., and STEWART, G. N.: Studies on Adrenal Insufficiency in Dogs, *Am. J. Physiol.*, **78**, 683, 1926; **84**, 649, 1928.
7. SAPHIR, O.: Myocarditis: A General Review with Analysis of 240 Cases, *Arch. Path.*, **32**, 1000, 1941; **33**, 88, 1942.
8. SAPHIR, O.: Meningococcus Myocarditis, *Am. J. Path.*, **12**, 677, 1936.
9. VANDER VEER, J. B., and NORRIS, R. F.: The Electrocardiographic Changes in Acute Pericarditis, *Am. Heart J.*, **14**, 31, 1937.

SPONTANEOUS PNEUMOTHORAX IN HEALTHY YOUNG ADULTS

WITH PARTICULAR REFERENCE TO THE ETIOLOGICAL RÔLE OF AERIAL ASCENT

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RECENTLY considerable interest has been manifested in the rôle of aerial ascent in precipitating spontaneous pneumothorax. Holter and Horwitz⁴ reported a case of spontaneous pneumothorax apparently precipitated by ascent to 8000 feet in an airplane. Lovelace and Henshaw,⁷ Todd,¹³ and others have described the effect of aerial ascent on patients with preëxisting pneumothorax. During the past year, 2 cases of spontaneous pneumothorax incident to altitude chamber flights were observed. One of these occurred during the flight; the other was present prior to the flight but symptoms were aggravated by the flight. It is the purpose of this paper to present these cases along with data concerning the incidence of spontaneous pneumothorax occurring during altitude chamber flights.

Incidence. In this study, the records of 86,916 man-flights in the altitude chamber were surveyed for the occurrence of spontaneous pneumothorax. The subjects were healthy, young combat bomber crew members. The "flight" consisted of a training flight of 90 minutes duration ascending from ground level (atmospheric pressure approximately 700 mm. Hg) to a simulated altitude of 30,000 feet (pressure 225 mm. Hg). The rate of ascent was approximately 2000 to 3000 feet per minute; peak altitude was maintained for approximately 15 minutes. In these 86,916 man-flights, spontaneous pneumothorax occurred in only one instance. In one other subject, symptoms due to a preëxisting partial pneumothorax necessitated descent from 17,000 feet.

A further survey was made of 771 individuals undergoing an explosive decompression "flight." This involves a change of altitude from 8000 feet (564 mm. Hg pressure) to 20-23,000 feet (349-307 mm.

Hg pressure) in less than 1 second, and simulates the effect of decompression by gunfire or flak of a pressurized cabin aircraft flying above 20,000 feet. In these 771 man-flights there was no instance of spontaneous pneumothorax. These findings are in accord with most data published to date on "explosive decompression." Sweeney¹² reported no evidence of pathological changes in explosive decompression of human subjects. Recently, however, Clark² reported 2 cases of mediastinal emphysema following explosive decompression of human subjects from a simulated altitude of 8000 feet to a simulated altitude of 31,000 feet in 0.5 second.

For purpose of comparison, a survey of the incidence of spontaneous idiopathic pneumothorax as compiled from the literature and the clinical records of the AAF Regional Hospital, Lincoln, Nebraska, was made. The term idiopathic spontaneous pneumothorax is applied only to those cases occurring in individuals in apparent good health with no evident pulmonary disease. Those cases secondary to some recognized underlying pulmonary disease such as tuberculosis or bronchial asthma are not included in this category. Jones and Gilbert⁵ in 1936 collected 19 cases of idiopathic pneumothorax recorded prior to that time. Babington¹ in 1944, reported 44 cases of idiopathic spontaneous pneumothorax, 31 of which were from the literature from 1935 to 1940. In a review of approximately 50,000 examinations of the chest Santos and Tanchanco^{10,11} found only 57 cases of idiopathic spontaneous pneumothorax, an incidence of only .11 %.

A survey of 28,000 admissions to AAF Regional Hospital, Lincoln, Nebraska, revealed 10 cases of spontaneous idiopathic pneumothorax (including the 2 herein reported); all were confirmed by Roentgen

ray. Of these 10 cases, 1 occurred during altitude chamber flight, 1 during sleep, 2 during walking, 1 while getting out of bed, and 1 while sitting at a desk; the activity of the remaining 4 patients was not recorded. In none of these individuals was there any evidence of tuberculosis, bronchial asthma, emphysema or other pulmonary disease. In 7 of the 10, there was no previous history of any pulmonary disease. Three gave a past history of "pleurisy" (2 with single episodes 3 years previously—1 with recurrent episodes for the preceding 6 years). The degree of collapse of the affected lung varied from 20% to 100%. All patients recovered with complete reëxpansion of the lungs in from 3 to 6 weeks. The duration of hospitalization varied from 16 to 56 days; the average stay was 32 days.

From these data, it would seem logical to conclude that changes of altitude encountered in normal aerial flight have no appreciable bearing on the precipitation of spontaneous pneumothorax in individuals with no apparent preëxisting lung disease. The occurrence of spontaneous pneumothorax during normal aerial flight is so rare that it is of no practical significance, and the impression that normal aerial flight is likely to produce spontaneous pneumothorax in a healthy individual is an erroneous one. The relationship between pneumothorax or pneumomediastinum and "explosive decompression" requires further study.

Case Reports. CASE 1. Pfc., aerial gunner, white, age 19.

History. This patient was admitted to the hospital Feb. 13, 1945, complaining of pain in the lower right chest. He stated that he was well until February 10. On that day while in the altitude chamber at 15,000 ft. he noticed the onset of moderate pain in the lower right chest aggravated by deep breathing and accompanied by moderate dyspnea. The patient was then descended to ground level in the lock, and the pain persisted for several hours. The following morning the pain had completely disappeared, and there was no recurrence on February 11 or 12. On February 13 the

patient again took an altitude chamber flight. At 18,000 ft. during ascent he noticed an aching pain in the lower right chest and again requested descent. Descent was begun at 18,000 ft., and the patient's symptoms disappeared completely at 17,000 ft. He had no pain after that time. He gave no history of diseases of the lungs or any previous serious illness or operation. Family history was irrelevant; there was no history of contact to tuberculosis.

Physical Examination. At the time of admission, physical examination revealed a thin, white male, not acutely ill, suffering no marked respiratory distress at the time. Pulse was 85 per minute, regular, and normal volume. Blood pressure was 118/83. Physical examination was negative except for lung findings as listed below.

Lungs: No lag or limitation of respiration was noted. There was slight decrease of tactile fremitus on the right side posteriorly. Percussion note was hyperresonant over the right side, both anteriorly and posteriorly. Normal vesicular breath sounds were heard over the entire left chest. Breath sounds were absent over the right chest anteriorly. Posteriorly, hollow tubular breath sounds were heard in the lower right chest near the midline. There was an absence of breath sounds over the remainder of the right chest. Egophony was noted over the same area as the tubular breathing.

Roentgen Ray Examination. Roentgen ray on February 13 showed typical partial pneumothorax of the right chest (Fig. 1). The lung was approximately 60 to 75% collapsed; there appeared to be some thickening of the bronchovascular markings on both sides. There was only slight displacement of the heart and mediastinal contents toward the left side.

Progress. The patient was kept at bed rest and was observed by physical examination and repeated Roentgen ray studies. By February 19 physical and Roentgen ray examination showed that the lung had begun to reëxpand (Fig. 2). On February 27 Roentgen ray examination showed approximately 85 to 95% reëxpansion of the lung. On March 9 normal vesicular breath sounds were heard over the entire right chest, and Roentgen ray examination showed complete reëxpansion of the right lung (Fig. 3). During this period of hospitalization, the patient remained symptom-free at all times. Blood

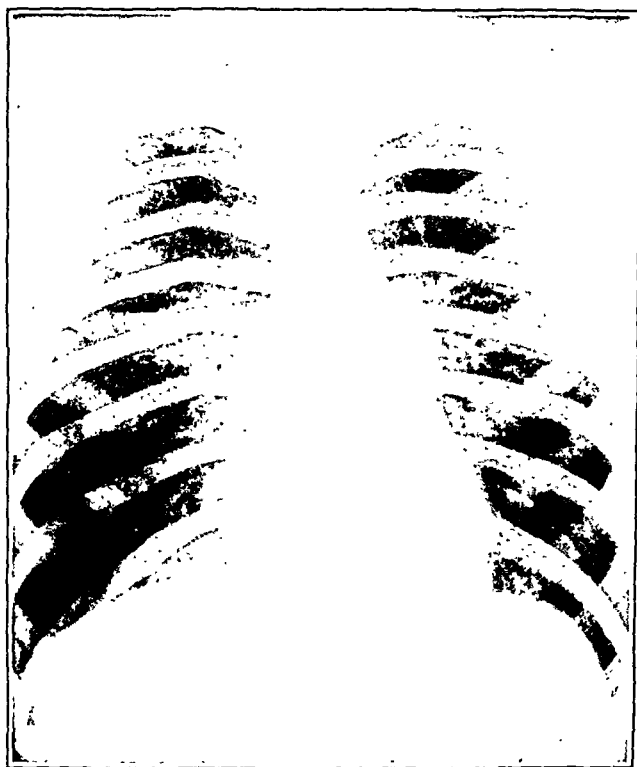


FIG. 1.—Day of admission, February 13. Shows partial pneumothorax on right side.

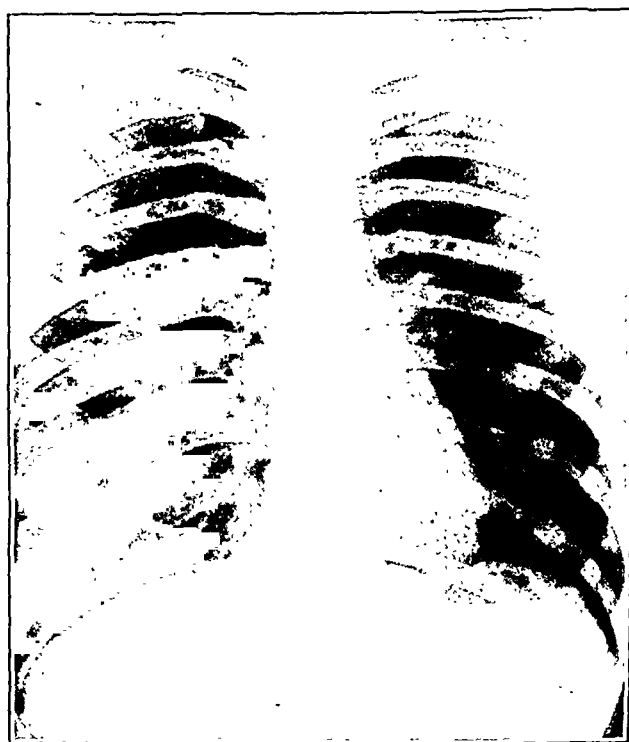


FIG. 2.—February 19, 1945. Shows beginning of reexpansion of right lung.

count, urinalysis, sedimentation rate and tuberculin test were normal.

CASE 2. Cpl., aerial gunner, age 19.

History. This patient was admitted on June 17, 1944, complaining of shortness of breath and pain in chest occurring during an altitude chamber flight the previous day. He stated that during ascent at 10,000 ft. he suddenly noticed difficulty in breathing and acute pain throughout the left chest. He gave a past history of having pneumonia 4 times as a child and being bothered with "pleurisy," especially on the left side, for

Physical Examination. On admission, physical examination was negative except for the chest findings as follows: There was a slight lag in the left chest. A friction rub was heard in the left axillary area and decreased breath sounds and increased resonance noted on the left chest laterally.

Roentgen Ray Examination. Roentgen ray on admission revealed a partial pneumothorax of the left side, the left lung being collapsed about 25%. There were some diaphragmatic adhesions. The right lung field was clear.

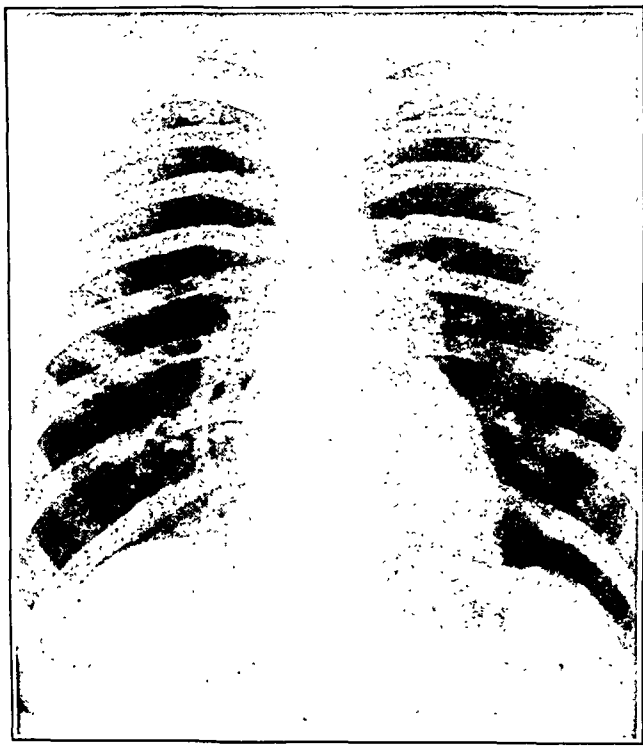


FIG. 3.—March 9, 1945. Shows complete reëxpansion of right lung.

the past 6 years. For 1 week prior to hospitalization the pain was localized in the left chest, and the patient had a chest Roentgen ray on June 12. This Roentgen ray showed partial pneumothorax on the left side and some pleural adhesions at the left base. The patient, however, was not aware of any abnormality prior to his chamber flight. He states that he was told that his chest Roentgen ray was negative. At any rate, the patient was permitted to make an altitude chamber flight on June 16 when a partial pneumothorax was noted on Roentgen ray on June 12.

Progress. During hospitalization the patient was treated symptomatically and kept at bed rest. The dyspnea and pain rapidly disappeared. The patient felt well during his period of hospitalization. On June 26, 1944, Roentgen ray examination showed that the pneumothorax on the left side was reëxpanded. The diaphragmatic adhesion still remained. Repeated sedimentation rates were normal. Repeated sputum examinations were negative for tubercle bacilli. Tuberculin skin test was negative and patient was discharged to duty on July 1, 1944.

Comments. The first of these cases illustrates a type of idiopathic spontaneous pneumothorax, apparently precipitated by simulated aerial flight. The mechanism of this phenomenon is not well understood. Common explanations of the mechanism of spontaneous pneumothorax are: (1) Rupture of an emphysematous bleb, or (2) Rupture of the visceral pleura. More recently Hamman³ has suggested that the initial lesion may be "interstitial emphysema of the lungs with an escape of air to the pleura through the mediastinum." Macklan⁸ has demonstrated air pathways along the vascular sheaths from the interstitial tissue to the mediastinum. The rupture of an emphysematous bleb at altitude due to the relative increase in pressure within the bleb, is easily understood. If such blebs were at all common, however, one would expect considerably higher incidence of spontaneous pneumothorax during aerial flight than that given above. It is difficult to see why the other mentioned mechanisms should be more common during aerial flight than during other activity. Certainly, we do not have sufficient data to speculate on the mechanism in this particular case. From the data presented, it seems likely that the occurrence of spontaneous pneumothorax during aerial flight is merely coincidental.

The second case illustrates a phenomenon which is much better understood and described—that of aggravation of preëxisting pneumothorax upon aerial ascent. Air within the pleural cavity responds to Boyle's law during ascent. The volume of this air will vary inversely with the absolute pressure of the atmosphere; or, if the volume remains stationary, the pressure exerted by this entrapped air will be increased. Therefore, a given degree of pneumothorax at ground level will produce progressively increasing degrees of lung collapse during ascent. This has been well shown by clinical and radiographic observation during altitude chamber flights,^{9,13} and its importance in aerial transportation of chest injuries pointed out.^{7,13} Todd¹³ on a basis of fluoroscopic

and Roentgen ray examinations at various altitudes has recommended that no person with pneumothorax ascend above 4000 feet. Lovelace and Henshaw⁷ have pointed out that the severity of symptoms of pneumothorax depends on the pressure involved and volume of the air in the pleural cavity; these, of course, vary with altitude.

Summary. 1. The records of 86,916 man-flights in altitude chambers were reviewed, revealing only 1 case of spontaneous pneumothorax.

2. Seven hundred and seventy-one "explosive decompression" altitude chamber flights were conducted with no incidence of pneumothorax. Study of the literature revealed 2 reported cases of mediastinal emphysema following "explosive decompression."

3. In a series of 28,000 hospital admissions, 10 cases of idiopathic spontaneous pneumothorax were found.

4. Two case records are presented: One of spontaneous pneumothorax occurring during a simulated aerial flight, and one of preëxisting pneumothorax with aggravation of symptoms during altitude chamber flight.

5. Discussion of possible mechanism of production of spontaneous pneumothorax is given.

Conclusions. 1. The incidence of spontaneous pneumothorax during simulated aerial flight is apparently no greater than that of idiopathic spontaneous pneumothorax occurring during other activities.

2. The common impression that spontaneous pneumothorax is likely to be caused by normal aerial ascent is an erroneous one, not supported by factual data.

3. The occurrence of spontaneous pneumothorax during normal aerial flight in individuals with no definite preëxisting lung disease is not common enough to be of practical significance.

4. In individuals with preëxisting pneumothorax, symptoms will be precipitated or aggravated by aerial flight. Such individuals should avoid flying, or if flying is necessary, should be restricted to low altitudes.

5. Spontaneous idiopathic pneumothorax in young adults is not of serious prognostic importance; complete reëxpansion of the collapsed lung usually occurs in 4 to 6 weeks.

6. The relationship between pneumothorax or pneumomediastinum and "explosive decompression" requires further study.

REFERENCES

1. BABINGTON, S. H.: Idiopathic Spontaneous Pneumothorax, *West. J. Surg.*, p. 73, Feb., 1944.
2. CLARK, D. M.: Mediastinal Emphysema (Pneumomediastinum) Following Explosive Decompression of Humans: Report of Two Cases, Memorandum Report TSEAL-3-695-291, AAAF Material Command, Jan. 1, 1945.
3. HAMMAN, L.: Spontaneous Mediastinal Emphysema, *Bull. Johns Hopkins Hosp.*, **64**, 1, 1939.
4. HOLTER, V. H., and HORWITZ, O.: Spontaneous Pneumothorax, *J. Am. Med. Assn.*, **127**, 519, 1945.
5. JONES, O. R., and GILBERT, C. L.: *Am. Rev. Tuberc.*, **33**, 165, 1936.
6. LEGGETT, E. A., MARS, J. A., and LEVINE, L.: Spontaneous Pneumothorax, *Am. Rev. Tuberc.*, **29**, 348, 1934.
7. LOVELACE, W. R., and HENSHAW, H. C.: Aerial Transportation of Patients, *War Med.*, **2**, 580, 1942.
8. MACKLAN, C. C.: Transport of Air Along Sheath of Pulmonic Blood Vessels From Alveoli to Mediastinal, Clinical Implication, *Arch. Int. Med.*, **64**, 913, 1943.
9. PATTERSON, E. W., RIPLEY, H. R., and MURPHY, D. R.: Investigation of Pneumothorax and Respiratory Function at Altitude, *Canad. Med. Assn. J.*, **50**, 520, 1944.
10. SANTOS, C., and TANCHONCO, F., JR.: Clinical Aspect and Incidence of Spontaneous Pneumothorax in 49,198 Fluoroscopic Examination, *Bull. Quezon Inst.*, **1**, 213, 1940; *Abstr., Radiology*, **37**, 118, 1941.
11. STEIN *et al.*: Spontaneous Pneumothorax, *War Med.*, **4**, 324, 1943.
12. SWEENEY, H. M.: Explosive Decompression, *Air Surg. Bull.*, **1**, 1, 1944.
13. TODD, G. S.: Effect of Altitude on Cases of Pneumothorax, *Lancet*, **2**, 20, 1943.
14. TROWBRIDGE, M.: Spontaneous Pneumothorax Complicating Bronchial Asthma, *Arch. Int. Med.*, **73**, 460, 1944.

WHY CERTIFIED MILK?*

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Why ask this question? This is not an argument for or against pasteurization, but I do hope to show that pasteurization is not the entire solution of the milk problem and that there are many reasons why certified milk is superior to other grades of milk on the market.

The fiftieth anniversary of Certified Milk† passed unnoticed in 1943. Its history is related in the first pages of *Methods and Standards for the Production of Certified Milk*. Throughout this period only 3 outbreaks of human disease have been attributed to Certified Milk: 1920, White Plains, N. Y. (diphtheria); 1924, New Rochelle, N. Y. (paratyphoid); 1926, Hamden, Conn. (septic sore throat). Perhaps as a result of these experiences and constant improvement in *Methods and Standards for the Production of Certified Milk*‡ there have been no outbreaks of disease attributed to certified milk since 1926. Previous to 1925 the public health reports of milk-borne disease are not very satisfactory. In this year the U. S. Public Health Service Milk Ordinance began to be adopted by various communities. Also since 1925 we have a complete file of *Reports of Disease Outbreaks Conveyed through Milk and Milk Products in the United States* as issued by the U. S. Public Health Service. It is from these reports that our statistical information has been obtained. The report for 1944 is not yet available.

During 19 years (1925-1943) there have been reported 819 milk-borne outbreaks, including 25 listed as "possibly conveyed through milk or milk products," an average of 43 per year. The maximum was 68

in 1926; the minimum 33, in 1932. Classified according to the kind of disease, the outbreaks were as follows:—

Typhoid fever	391
Gastro-enteritis and food poisoning	183
Streptococcal	184
Brucellosis	31
Dysentery	15
Diphtheria	15
	<hr/>
	819

Classified according to the kind of milk or milk product involved, the outbreaks were as follows:—

Certified (raw)	1
Other raw ¹	712
Pasteurized	62
Canned	3
Boiled	2
Unknown	39
	<hr/>
	819

¹ Those outbreaks reported as due to both raw and pasteurized milk are included under "raw" only; there were 7 such.

In 1940 it was stated¹ that "Epidemics of the types outlined recur year after year, even from certified and grade A raw milk." . . . "Even certified raw milk has been responsible for outbreaks." In view of the statistics presented above, is this generous use of plurals and "year after year" applicable to Certified Milk? Continuing: "It is a most significant fact, however, that no outbreak has ever been reported as due to grade A pasteurized milk in any city operating under the milk ordinance recommended by the Public Health Service." The statement was carefully worded to exclude all but grade A pasteurized milk and, apparently, was based upon data available through 1938. Since then there have been 5 outbreaks

* Abstract of a talk before the Milk Commission of the Philadelphia Pediatric Society, February 20, 1945.

† These words are capitalized as the name is copyrighted in this form

‡ *Methods and Standards*, 1928, was the first milk control manual in which directions were published for the recognition of the hemolytic streptococci of septic sore throat.

attributed to grade A pasteurized milk in communities operating under the Public Health Service ordinance. If all kinds of milk recognized under the ordinance are considered, there have been over 60 outbreaks (12 attributed to pasteurized milk or products) since 1925. The ordinance has been in effect in 1181 communities for varying lengths of time and doubtless has been beneficial. It includes recognition of Certified Milk the public health record of which is unsurpassed by that of any other grade of milk, raw or pasteurized.

As may be noted in the first tabulation above, 93 % of the reported outbreaks of milk-borne disease are of typhoid fever, streptococcal disease (septic sore throat and scarlet fever) and gastroenteritis (food poisoning). Until 1935 typhoid fever constituted more than 50 % of milk-borne outbreaks. Because of the decline in the typhoid rate in the population at large due to many factors, such as improved water supplies, anti-typhoid vaccination, and increase in pasteurization of milk, typhoid constituted only 12 % of milk-borne outbreaks of disease in 1942 and 1943. The incidence of milk-borne streptococcal outbreaks was above 30 % in 1929, and above 40 % in 1936, but has declined fairly consistently since then to 10 % in 1943. Contrasted with these, the incidence of gastroenteritis attributed to milk and milk products has risen from a level of less than 15 % previous to 1935 to 62 % in 1943. Although this reported increase may be due to better diagnosis, especially to the recognition of staphylococcus enterotoxin as a cause of food poisoning, it is clearly established that since 1938 gastroenteritis has occupied first place among milk-borne diseases.

Udder and teat canal infections with staphylococci are very common, even in the absence of clinically recognized mastitis. Unless the dairy farm is engaged in the effort to produce raw milk of very low bacterial count, such as Certified Milk, cows harboring staphylococci are of little

or no concern to the dairyman. Many of these staphylococci are indistinguishable from the enterotoxin-producing staphylococci which cause food poisoning. Milk seeded with these organisms may, by improper handling (inconstant or insufficient refrigeration), serve as culture medium in which the toxin content rises to a pathogenic level. The avoidance of such accidents is complicated by the heat resistance of staphylococci and their enterotoxin. Some strains of staphylococci survive heating at 60° C. for nearly 1 hour and it is possible to recover living staphylococci from many samples of market milk which have been pasteurized at 62° C. for 30 minutes and with negative phosphatase reactions. The enterotoxin resists heating at 95° C. for 20 minutes. From 1933 to 1943 inclusive, the U. S. Public Health Service reports record 126 outbreaks of gastroenteritis or food poisoning, excluding those attributed to chemical substances and paratyphoid organisms. Of these, 79 were attributed to raw milk or milk products, 27 to supposedly pasteurized milk or products, 1 to boiled milk, 2 to canned milk, and 17 to milk of unknown processing. In nearly half of these outbreaks staphylococci were known to be involved and in most of the others clinical evidence indicated staphylococcus enterotoxin. In many instances the dairy product was contaminated subsequent to milking, after pasteurization, or during food preparation. In other instances cows with staphylococcus mastitis were incriminated. Obviously, cows shedding staphylococci in their milk and milkers with staphylococcus infections of the hands are potentially dangerous, whether the milk is to be pasteurized or not. Undoubtedly, the time-honored broad requirements of healthy animals, healthy milkers, and cleanliness have had much to do with avoiding any outbreak of food poisoning attributable to Certified Milk.

The public has been bombarded with sensational articles in popular magazines*

* ADDENDUM: See Raw Milk Can Kill You, Coronet, May 1945. Correspondence with the author of this article reveals that the outbreak at "Crossroads, U. S. A., in one of those states in the Midwest," was fictitious, representing no actual occurrence, and, presumably was described merely to illustrate what the author thought might happen.

creating the impression that anyone who drinks a glass of raw milk is in imminent danger of contracting undulant fever and that if all milk were pasteurized there would be no human brucellosis. Neither proposition is true. In a review of Immunity in Brucellosis Huddleson⁵ (1942) has stated:

"When human beings are exposed to brucella, a large percentage of those exposed fail to show any clinical evidence of the disease, but do develop specific serum antibodies and skin sensitivity, and in some instances to the same degree as those clinically infected. . . . When antibodies or skin sensitivity are found present in healthy persons a state of active immunity is indicated."

Another factor also helps to explain the low incidence of undulant fever among consumers of milk infected with *Brucella abortus*; the dosage factor. This was beautifully demonstrated by an outbreak in an institution using raw milk from its own infected dairy herd.⁴ Some of the kitchen help and others having access to an abundance of cream acquired brucellosis. Some hundreds of inmates drinking the whole (or partially skimmed?) milk suffered no ill effects. It has long been known that brucella organisms are more numerous in gravity cream than in the underlying milk. Also the dilution factor is involved in the dosage factor. In outbreaks involving fairly large milk supplies the incidence of human infection is often in the neighborhood of 1.5% of the consumers of the milk. In family outbreaks, in which all of the milk may come from a single heavily infected cow, several members may become infected.

Brucella suis is more virulent for man than is *Brucella abortus*. Hardy² (1943) states:

"It is still evident that in the United States the incidence of recognized brucellosis in man tends to vary directly with the extent of the hog-raising industry. . . . It was previously assumed, as a result of the studies of the Mediterranean Fever Commission, that brucellosis was acquired

through the ingestion of infected raw dairy products. It has since been established through experimental study and the interpretation of epidemiological observations that the infection may readily be acquired through cutaneous contact with infective secretions, excretions, or tissues. This appears to explain the ease of infection of bacteriologists, who are generally able to avoid the ingestion of those organisms with which they work but can scarcely hope to prevent entirely the contamination of fingers and hands. The high incidence of infection in packing-plant employees is readily understood when it is known that *Brucella* may penetrate the normal or minutely abraded skin. Likewise the high rate of infection in men on the farm, as compared with the women, can be explained only as a result of the more common skin contamination by infective discharges of cattle or hogs."

Although hogs are resistant to *Brucella abortus*, cattle in close association with hogs occasionally become infected with *Brucella suis*. In the two milk-borne outbreaks reported by the U. S. Public Health Service (1941 and 1942) as due to *Brucella suis*, the incriminated cows had been allowed to run with infected hogs in the same lot. Reports from Iowa (Hardy, Jordan and Borts,³ 1936) and Alabama (Annual Report, Bureau of Laboratories, Alabama State Department of Health, 1943) indicate that about 70% of human brucellosis in those states is due to *Brucella suis*. In states where there is little hog raising, more of the human brucellosis is caused by *Brucella abortus*. According to Hardy, Jordan and Borts, in the West North Central states the incidence of clinically recognized brucellosis per 100,000 population was about 4 persons and in New England less than 2. There is no reason to believe that this incidence has materially changed since 1936.

"In the case of human beings, it has been observed repeatedly in many laboratories that those who have developed an immunity as a result of a clinical or sub-clinical infection with one species, may

freely work with the others without becoming infected." (Huddleson,⁵ 1942,)

We are confronted by a public health dilemma. The pasteurization of all milk might reduce the incidence of human brucellosis 50%; on the other hand, it might reduce the number of immunized persons in the population to such an extent that there would be an increased incidence of clinical brucellosis, especially in those occupations and regions where exposure to cutaneous infection with *Brucella suis* is a major factor. Certified Milk follows the program of eliminating brucellosis from its dairy herds and of prohibiting the mingling of cows with hogs and other animals. Under these conditions it is very improbable that an infective dose of *Brucella* organisms will ever gain entrance to Certified Milk.

It has been said¹ that "the one thing which differentiates pasteurization from all other protective measures is that while all other measures *may fail* to protect completely even if they are properly applied, pasteurization *will always* protect if it is properly applied." Without detracting from the value of pasteurization, 3 comments may be made: (1) Since 1926 "*other measures*" have given complete protection to the consumers of Certified Milk; (2) Pasteurization, properly applied, does not destroy some of the enterotoxic staphylococci; (3) Even with the best of intentions and equipment, pasteurization is not always properly applied. This is why it is required that Certified Milk-pasteurized must be Certified Milk before it is pasteurized; it has a double safe-guard enjoyed by no other grade of milk. Certified Milk-raw is required to have a lower bacterial count than are other grades after pasteurization. True, many samples of grade A pasteurized milk have low bacterial counts rather than counts just below

the legal limit of 30,000 per cc., but how is the consumer to know which samples these are since there is nothing on the labeling to distinguish a milk with 500 bacterial colonies per cc. from one which may have a count of 30,000 per cc. unless it is certified? These are some of the reasons *why certified milk*. Others may be found in the Methods and Standards for the Production of Certified Milk, such as:

Segregation of the dairy cows from other farm animals, especially hogs.

Frequent testing of milk whey and the serum of cows for *Brucella* agglutinins and prompt elimination of reacting animals.

Frequent tuberculin testing of cattle.

The control of bovine mastitis.

The dairy herd under the regular supervision of a designated veterinarian.

All employees subject to weekly medical inspection by a designated physician who also makes such medical examinations and requires such laboratory tests (fecal cultures, throat cultures, etc.) as he may think advisable or as may be required by the Commission. Medical examination of all new employees.

Weekly or more frequent bacteriological examination of the milk. Control of coliform and spore-forming bacteria.

Cleanliness of the stables, milking operation, and milk-handling. Frequent inspections by a designated sanitary inspector.

There are no secret or proprietary methods for the production of Certified Milk. Any dairyman may follow the Methods and Standards but has he the facilities for doing so without the services of a Medical Milk Commission and has the public the assurance that he does so without the certification of a Commission? Is such a milk required to be produced, processed and bottled at a farm so identified on the bottle cap, or is it mixed with other milk before it reaches the consumer?

The author is very grateful to Mr. A. W. Fuchs and to the late Mr. Leslie C. Frank of the U. S. Public Health Service, who for many years have kindly supplied me with the reports discussed. I have quoted freely from my contributions to the manuscript for a book on Bovine Mastitis, A Symposium, edited by R. B. Little and W. N. Plastringe, and soon to be published by the McGraw-Hill Book Company, Inc., New York.

REFERENCES

1. FUCHS, A. W.: Milk and Its Relation to Disease, delivered before Philadelphia College of Physicians, Feb. 5, 1940.
2. HARDY, A. V.: *In* Huddleson, I. F., Brucellosis in Man and Animals, New York, The Commonwealth Fund, 1943.
3. HARDY, A. V., JORDAN, C. F., and BORRS, I. H.: Undulant Fever; Further Epidemiological and Clinical Observations in Iowa, J. Am. Med. Assn., **107**, 559, 1936.
4. HARING, C. M.: Personal communication.
5. HUDDLESON, I. F.: Immunity in Brucellosis, Bact. Rev., **6**, 111, 1942.

AMINO ACIDS IN THE PRODUCTION OF PLASMA PROTEIN AND NITROGEN BALANCE

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PHYSICIANS and investigators are acutely interested in the various uses of whole blood, blood plasma, and plasma substitutes in emergencies, battle injury, burns, chronic infection and protein depletion due to starvation or disease. Much work is being done on plasma substitutes, but as a rule these substitutes at best can tide the body over an emergency of a day or so to permit the normal production of plasma protein within the body to be resumed. Obviously it is far better for the body to produce its own plasma proteins than to receive them from outside, though plasma proteins introduced parenterally can supply all the protein needs of the body over many weeks.⁴ The plasma proteins supply much of the cell protein requirements and are in a constant state of depletion and repletion.⁶ The repletion of plasma proteins comes largely from the liver. The body makes its own plasma protein from reserve stores in emergencies or from the incoming diet proteins normally. The body can make plasma proteins and maintain nitrogen balance when the sole source of nitrogen is a protein digest or a mixture of the 10 amino acids²¹ essential for growth.

Fortunately for us, this laboratory has been enabled to use pure crystalline amino acids* in various mixtures, parenterally or by mouth, to study plasma protein production and nitrogen balance first in dogs and subsequently in man. This report includes material from various papers recently published—method details, amino acid mixtures and related histories must be consulted in the original papers.

Amino acids (10 of the more than 20

found in natural proteins) were shown by Rose and associates²¹ to be required for satisfactory growth in rats. These 10 essential amino acids were: threonine, valine, leucine, isoleucine, lysine, tryptophane, phenylalanine, methionine, histidine and arginine. It was shown later in this laboratory^{11,16} that these same amino acids parenterally in dogs as the sole source of nitrogen will cause ample *new plasma protein* production. This is comparable to the response following a similar nitrogen intake of some good natural diet protein.

Intensive study of the amino acids as they are used in the body economy is very much to be desired. Many laboratories will be increasingly occupied with these problems in the near future. We know very little about the influence of single amino acids upon body metabolism but recent work with methionine^{7,18} and cystine (Table 1) are intriguing. It is at least possible that variable mixtures of amino acids may have specific effects on body metabolism in health and in diseased states. The possibilities here are too numerous to be discussed but the call for more investigation is obvious. It is our conviction that in these dog experiments (Tables 1 to 3) the various introduced amino acids are largely assembled in the liver to form plasma proteins which may then be used to supply body protein needs, rather than that each cell picks up the amino acids from the blood to make its own specific cell protein.

The production of new plasma protein in dogs is known to be directly related to the kind and quantity of the diet protein

* We are indebted to Merck & Company, Inc., for a generous supply of pure amino acids.

intake.⁸ This observation is based upon tests in standardized hypoproteinemic dogs, depleted of circulating plasma protein and reserve protein by bleeding followed by immediate return of red blood cells suspended in saline (plasmapheresis). If the diet protein intake be limited to 1 gm. per kilo body weight, the daily removal by this plasmapheresis procedure of about 20 % of the circulating plasma will reduce the plasma protein level from the normal of 6 to 7 % to 4 % in 1 to 3 weeks. At this hypoproteinemic level plasma protein regeneration is strongly stimulated, but with the low protein intake the daily amount of plasma removal must soon be reduced to about 10 % of the total circulating protein. Subsequent variations in the kind and quantity of the protein intake are reflected in the amount of plasma protein which must be removed to maintain a steady hypoproteinemia. Many tests of food proteins and several of amino acid supplementation of food proteins have been previously reviewed.¹⁴

intake from higher to lower. Also the nitrogen balance was negative. A sharp decline in plasma protein production occurred in Period 19 with zero diet protein intake.

Cystine added in Period 20 boosted the plasma protein production. It was a short-lived stimulation, gone by Period 21, but offers food for speculation regarding internal metabolism. Moreover, it is practical evidence of the possible pitfalls in any conclusions drawn from short-term experiments. It is obvious that *more* than cystine went into the plasma protein produced. If a supposedly complete mixture of amino acids had been given with the cystine, credit might have been given to the mixture rather than to the cystine. A complete mixture except for *cystine* substituting for *methionine* by mouth again stimulated plasma protein output in Period 22. But weight loss occurred and the test could not be continued. A completely adequate source of protein nitrogen

TABLE 1.—AMINO ACIDS IN PLASMA PROTEIN PRODUCTION
Ten Essentials (Va, Vb) Very Effective Orally or by Vein

(Dog 41-187)

Period (7 days)	Diet	Nitrogen intake		Urine nitrogen (gm.)	Plasma protein removed (gm.)	Plasma protein level (%)	Weight (kg.)
		Amino acids (gm.)	Basal (gm.)				
18	Liver		11.2	15.3	22.2	3.99	10.2
19	Protein-free		0.1	10.1	3.7	3.99	9.9
20	Protein-free + cystine	0.8	0.3	5.0	14.1	4.15	9.5
21	Protein-free + cystine	0.8	0.3	4.5	1.8	3.76	9.3
22	Amino acids VI	18.5	0.3	18.7	18.3	4.39	9.0
25	Amino acids Va	18.3	0.3	7.7	15.3	4.27	9.2
26	Amino acids Va	18.3	0.3	9.0	15.3	4.10	9.3
27	Amino acids Vb minus glycine	12.4	0.3	7.9	17.6	4.01	9.0
28	Amino acids Vb minus threonine	18.1	0.3	17.4	8.4	3.90	9.2
29	Amino acids Vb, i.v.	16.7	0.3	17.1	16.3	4.27	9.0
30	Amino acids Vb—VII, i.v.	18.3	0.3	15.5	16.1	4.01	8.4

The 10 essential amino acids were found to be effective in plasma protein production in dogs.¹¹ Table 1¹¹ contains portions of the published data from a continuous 30 week study. The plasma protein removed in the 18th week was more than that which could be related to the current liver protein intake of 70 gm. (11.2 gm. nitrogen \times 6.25). The immediately preceding weeks afforded a much higher protein intake and this *carry over* in production is expected with any change of protein

had not been provided in Period 22. Nitrogen balance was slightly negative.

When the 10 essential amino acids plus glycine were provided by mouth as noted in Periods 25 to 27, Table 1, positive nitrogen balance and plasma protein production were good. Throughout all the tables the mixtures designated by the Roman numeral V contained the 10 essentials plus glycine.¹¹ The modifying letters indicate variations in proportion or form. For example, Vb was the same as Va

except that the l(-)-leucine in Va was replaced by double the quantity of dl-leucine. The good production of plasma protein in Weeks 25 and 26 continued in Week 27 when the glycine was omitted. Production dropped sharply, however, when *threonine* was omitted.

Given by *vein*, the amino acids including *threonine* supported a return of plasma protein production, Table 1. But weight declined and nitrogen balance was questionably maintained. The excellent tolerance to the amino acid mixtures prompted further trials by vein.

at the end of the 30 weeks was 11.3 kg. Various slight modifications of the 10 essential amino acid mixtures are indicated in Table 2, second column. Details are given in an earlier article¹⁶ which adds other confirmatory data.

Comparison of utilization of amino acids given by *oral* administration with that of *parenteral* administration is of interest. Such an experiment is presented in Table 3⁹ from a recent report. The differences are not large, but it appears definite that the *oral route favors superior utilization for plasma protein formation and for nitrogen*

TABLE 2.—TEN ESSENTIAL AMINO ACIDS IN PLASMA PROTEIN PRODUCTION GIVEN INTRAVENOUSLY, SUBCUTANEOUSLY, OR INTRAPERITONEALLY

(Dog 41-187)

Period (7 days)	Amino acid mixtures	Nitrogen intake		Urine nitrogen (gm.)	Plasma protein removed (gm.)	Plasma protein level (%)	Weight (kg.)
		Amino acids (gm.)	Basal (gm.)				
4	Vg, i.v.	18.7	0.3	15.4	23.5	4.14	11.9
5	Vg, i.v.	18.7	0.3	14.4	18.1	3.85	11.8
6	Vg, i.v.	18.7	0.3	14.6	14.6	3.90	11.5
7	Vg, s.c.	18.7	0.3	12.0	12.9	3.91	11.8
8	Vj, s.c. (Vg with less glycine)	11.1	0.3	7.2	15.0	3.98	11.7
9	Vj, s.c.	11.1	0.3	6.6	17.0	3.89	11.6
10	Vm, s.c.	12.4	0.3	6.8	11.0	3.82	11.7
11	Vm, i.p.	12.4	0.3	10.2	18.6	4.02	11.3
12	Vo, s.c.	13.3	0.3	8.9	16.3	3.92	11.1

TABLE 3.—TEN ESSENTIAL AMINO ACIDS IN PLASMA PROTEIN PRODUCTION—ORAL AND PARENTERAL ADMINISTRATIONS COMPARED

(Dog 42-1081)

Period (7 days)	Amino acid mixture	Nitrogen intake		Urine nitrogen (gm.)	Plasma protein removed (gm.)	Plasma protein level (%)	Weight (kg.)
		Amino acids (gm.)	Basal (gm.)				
13	Casein	..	21.2	13.0	19.4	4.33	8.8
14	Vah, s.c.	18.0	3.6	20.6	13.9	4.03	9.1
15	Vah, s.c.	18.0	3.6	14.4	13.2	4.15	9.1
16	Vah, oral	18.0	3.6	12.3	15.2	4.14	9.0
17	Vah, oral	18.0	3.6	12.1	24.7	4.30	9.0
18	Vah, i.v.	18.0	3.6	17.0	14.9	4.19	8.9
19	Vah, i.v.	18.0	3.6	18.0	15.8	4.11	8.9
20	Vah, s.c.	18.0	3.6	15.1	17.9	4.12	9.3
21	Vah, s.c.	18.0	3.6	16.2	14.7	4.10	9.4

The ease of use and effectiveness of amino acids given *parenterally* were convincingly shown in the observations of Table 2,¹⁶ part of a continuous 30 week period of parenteral nitrogen administration. There was no question here of maintenance of positive nitrogen balance. Injections by vein, subcutaneously, and into the peritoneal cavity were all well tolerated and well conserved for nitrogen needs, including ample production of plasma protein. The slight weight loss in these earlier periods was corrected later when larger intakes were given and the weight

balance. Other observations such as those in Table 1 and those in man as presented below confirm this difference.

The better conservation of nitrogen after oral intake is usually more definite than the difference in plasma protein production. This conservation is reflected chiefly in the urinary constituents other than urea and ammonia. The difference is also obtained when protein digests are compared orally and parenterally.^{10,13,17} Escape of amino acids into the urine no doubt is part of the explanation but other factors are probably involved. Whereas

we have found that the total undetermined urinary fractions (*i. e.*, non-urea-and-ammonia) are similar for comparable injections of amino acid mixtures and protein digests, others¹ have noted that urinary amino acids are lower after injection of protein digests. It would appear that other fractions of the undetermined nitrogen group increase more after digest injection than after amino acid injection to account for the equality of the totals. It is fair to say that different protein digests vary in composition and different findings from various laboratories may reflect some of these differences.

The good utilization of synthetic mixtures made up largely of *synthetic amino acids* is somewhat surprising. Undoubtedly some of the urinary nitrogen after parenteral injection of mixtures containing 6 or 7 amino acids, half of which consist of the optical forms not found in natural proteins, contains *some of these unnatural isomers*. It is believed that in rats the first 5 of the 10 essentials as listed above are utilizable upon oral intake only in their natural forms.²¹ In the rat some d(+)-leucine may be converted to the natural form¹⁹ but apparently most of unnatural lysine is excreted as such.²⁰ In mice²⁴ and in man^{1,22} unnatural tryptophane appears *not* to substitute upon oral intake for the natural form and to be associated with the appearance of an uncommon indole derivative in the urine. Moreover, in man feeding of racemic phenylalanine is followed by greater loss of phenylalanine into the urine than is noted after ingestion of the natural form.¹

This information about unnatural isomers is of biochemical interest and some physiologic importance but does not justify conclusions as to *toxicity*. No demonstration of real toxicity to unnatural or natural amino acids in the mixtures, the concentrations, and the quantities used in our observations has been found. Certain transient intolerances have been studied. The subject of *tolerance* to amino acid mixtures is important. *Tolerance* and *toxicity* overlap and are difficult to define.

We recognize that almost any substance in high enough quantity may be poisonous. But because an artificial diet containing 10% methionine may be injurious⁵ it is not to be concluded that the 3% methionine in milk protein is 30% as injurious! In studying tolerances to the intravenous injection of amino acid mixtures and protein digests we have been concerned with *transient disturbances*, chiefly nausea and vomiting.

No evidence of serious or persistent injury has ever been noted after any of hundreds of injections into animals and man using the materials here studied. A recent report on *tolerance* to amino acid injection emphasizes the low tolerance to mixtures containing *glutamic acid*.¹⁵ *Aspartic acid* is likewise prone to stimulate vomiting.^{9,15} Proper mixtures of the 10 essential amino acids are much better tolerated than any protein digests which contain high contents of glutamic acid, such as casein digests. Some data have been presented indicating improved tolerance to the 10 essentials by the addition of glycine.¹⁵ In certain quantities alanine, serine, proline, and hydroxyproline were also found to be well tolerated in the mixtures.

A mixture which could be injected into dogs at rates greater than 10 mg. nitrogen per kilo per minute in quantities greater than 300 mg. nitrogen per kilo consisted of dl-threonine 7, dl-valine 15, l(-)-leucine 10.9, dl-isoleucine 9.9, l(+)-lysine.HCl.H₂O 10.9, dl-tryptophane 3, dl-phenylalanine 9.9, dl-methionine 6, l(+)-histidine.HCl.H₂O 5, l(+)-arginine.HCl 5, glycine 9.9, dl-a-alanine 4, dl-serine 2, l(-)-cystine 0.5, and l(-)-tyrosine 1 (all given in %). This exact mixture has not been tested in man.

Solutions of crystalline amino acids can be injected subcutaneously in relatively high concentration without disturbance. In dogs and man¹⁰ more than 10% solutions in distilled water are well tolerated. In premature infants absorption of such concentrated solution is slow and a more dilute solution is to be preferred.

The first data in man on the prolonged

use of crystalline amino acids for parenteral feeding are summarized in Table 4.² The mixtures used consisted of the 10 essentials plus glycine and were given intravenously and subcutaneously. The caloric intake during the first 5 days was less than 800 calories per day and nitrogen balance was not obtained until Periods 2 and 3 when the caloric total daily was above 1200. A modest nitrogen intake needs a certain caloric protection by carbo-

and 9, total nitrogen retention became greater, largely by the reduction in the undetermined urinary nitrogen fraction. Explanation of this change has been discussed above. The patient made a surprising recovery based upon successful surgery made possible largely by pre-operative parenteral feeding.

Amino acids parenterally were virtually the sole source of nitrogen in Period 1 from a recent report reproduced in Table

TABLE 4.—TEN ESSENTIAL AMINO ACIDS PARENTERALLY IN MAN—
POSITIVE NITROGEN BALANCE AND WEIGHT GAIN

F. K., age 63; pyloric ulcer with obstruction.

Period (5 days)	Amino acids	Nitrogen intake		Nitrogen output				Nitrogen balance*	Weight (kg.)
		Amino acids (gm.)	Basal (gm.)	Urine total (gm.)	Urine urea- NH ₃ (%)	Urine undeter- mined (gm.)	Feces (gm.)		
1	Vh, i.v., s.c.	73.5	0.5	86.5	78	19.7	0.9	-15.8	44.1
2	Vh, i.v., s.c.	88.3	5.4	88.1	72	24.8	0.9	+ 3.7	46.0
3	Vn, i.v., s.c.	73.1	7.2	76.9	72	21.8	0.9	+ 1.6	44.2
4	27.2	33.3	84	5.2	1.9	-10.7	43.5
Interval of 21 days, with subtotal gastrectomy on 9th day.									
5	Vn, i.v., s.c.	72.9	13.7	68.0	71	19.3	7.4	+11.2	41.6
6	Vx, i.v., s.c.	64.4	17.4	53.9	67	17.9	7.3	+20.6	43.3
7	Vx, i.v., s.c.	65.5	16.7	59.4	66	20.0	7.7	+15.1	43.9
8	80.0	44.3	83	7.6	7.5	+28.2	45.9
9	80.0	42.9	84	7.0	8.5	+28.6	47.0

* Nitrogen of vomitus and Wangenstein drainage deducted.

TABLE 5.—TEN ESSENTIAL AMINO ACIDS PARENTERALLY YIELD NITROGEN BALANCE AS
SOLE SOURCE OF NITROGEN

J. S., age 21, chronic ileitis with obstruction.

Period (5 days)	Amino acids	Nitrogen intake		Nitrogen output				Nitrogen balance*	Weight (kg.)
		Amino acids (gm.)	Basal (gm.)	Urine total (gm.)	Urine urea- NH ₃ (%)	Urine undeter- mined (gm.)	Feces (gm.)		
1	Vu, i.v., s.c.	130.0	0.6	108.4	57	46.1	11.2	+ 8.4	38.9
2	Vu, i.v., s.c.	65.2	3.4	64.7	60	25.8	5.8	- 1.9	38.6
3	Vu, i.v.	65.3	8.3	54.0	57	22.9	11.8	+ 6.6	38.6
4	(Operation)	0	16.5+	22.1	76	5.4	37.1
5	Vu, i.v.	91.7	2.2	82.1	61	31.9	6.0	+ 5.8	37.2
6	None	0	78.3	31.6	79	6.6	10.3	+36.4	37.2

H. S., age 55, carcinoma of head of pancreas.

1	Vua, i.v., s.c.	59.2	0.2	68.4	76	16.5	4.7	-14.8	60.4
2	Vub, s.c.	58.3	0.0	52.3	68	16.7	6.3	- 1.8	

* Nitrogen of vomitus and Wangenstein drainage deducted.

hydrate. It would be an interesting experiment to test whether or not nitrogen balance might be obtained from a sufficiently high intake of pure amino acids in the total absence of carbohydrate and fat. In the observations of Table 4, Periods 5 to 7, when the caloric intake was an ample 2000 to 3300 calories daily, nitrogen balance was strongly positive and weight gain considerable. With return to a diet of natural protein in Periods 8

5.¹⁰ With the high intake, balance was positive—evidence that the 10 essential amino acids plus glycine given parenterally are alone adequate for the nitrogen requirements of man. This patient, J. S., 21 years, was severely depleted of body protein. Nitrogen balance was continued during parenteral injections during Periods 2 and 3, but was impossible due to poor food intake and vomiting when oral feeding was attempted in Period 4. Recovery

from resection of a segment of ileum at the end of Period 4 was uneventful. Nitrogen balance was continuous in Period 5. Better utilization of natural food protein by mouth is again demonstrated in Period 6.

Patient H. S., 55 years, the second patient in Table 5, received the amino acid solution almost entirely *subcutaneously*, partly because suitable veins were difficult to find. Nitrogen balance was

total weight gain was 10 kilos and the clinical improvement in the ulcerative colitis was marked. Abdominal distress and diarrhea disappeared although the colon lesions remained. Reduction in fecal nitrogen was considerable from the high level of Period 1.

Tolerance to the mixture Vuj was only moderately better in this patient of Table 6 than to Amigen. There was nausea and vomiting with too rapid injections of vari-

TABLE 6.—TEN ESSENTIAL AMINO ACIDS PARENTERALLY LONG CONTINUED—WITH NITROGEN BALANCE AND WEIGHT GAIN
M. E., age 26, chronic ulcerative colitis.

Period (5 days)	Amino acids	Nitrogen intake		Nitrogen output			Nitrogen balance (gm.)	Weight (kg.)
		Food (gm.)	Amino acids (gm.)	Urine total (gm.)	Urine urea- NH ₃ (%)	Urine undeter- mined (gm.)		
0								52.26
1	None	101.5	..	49.5	81	9.3	+12.3	52.09
2	Varies, i.v.	6.5	68.0	68.3	72	18.9	-20.3	50.23
3	Amigen, i.v.	15.2	62.6	56.6	67	18.9	+ 8.7	53.63
4	Vuj, i.v.	15.2	59.9	55.7	69	17.4	+ 4.7	54.12
5	Vuj, i.v., s.c.	7.5	102.0	93.4	73	25.5	- 2.6	52.18
6	Vuj, i.v., s.c.	13.9	85.6	82.4	69	25.3	+ 3.5	54.43
7	Vuj, i.v.	12.0	84.0	80.9	70	24.0	+ 6.0	53.43
8	Vuk, i.v.	7.4	85.9	76.2	68	24.5	+ 3.1	54.63
9	Vuk, i.v.	6.9	43.1	44.3	61	17.3	- 8.0	55.91
10	Vuj, i.v.	6.9	43.1	37.0	60	14.9	- 0.8	57.19
11	Vuj, s.c.	6.9	43.2	36.4	65	12.8	+ 0.5	58.19
12	Vuk, oral	6.9	43.3	25.1	49	12.7	+ 8.1	58.28
13	Vuk, oral	6.9	43.3	27.7	49	14.1	+ 6.4	59.09
14	Vuk, oral	6.9	43.3	27.4	48	14.2	+ 9.0	59.83
15	Vuk, i.v.	6.9	43.3	38.2	63	14.2	lost	60.08
16	Vuk minus histidine, i.v.	6.9	40.7	37.8	63	13.9	- 5.2	60.78
17	Vuk minus histidine, i.v.	6.9	40.7	41.0	66	14.0	- 5.1	61.27
18	Vuk, i.v.	6.9	43.1	36.2	61	14.2	+ 1.8	62.13
19	None	101.5	..	61.7	85	9.1	+32.3	62.50
20	None	101.5	..	65.0	87	8.3	+25.0	63.21

TABLE 7.—TEN ESSENTIAL AMINO ACIDS BY MOUTH COMPARED WITH AMIGEN AND EGG
M. E., age 26, chronic ulcerative colitis.

Period (10 days)	Diet	Nitrogen intake		Nitrogen output			Nitrogen balance (gm.)	Weight (kg.)
		Amino acids (gm.)	Basal (gm.)	Urine total (gm.)	Urine urea- NH ₃ (%)	Urine undeter- mined (gm.)		
1	Vuj	85.6	5.0	81.3	72	22.5	-28.5	58.6
2	Vuj	86.6	5.0	53.3	65	18.6	+ 2.6	59.3
3	Vuj	86.6	5.0	54.2	64	19.6	+ 2.1	59.5
4	Amigen	90.0	5.0	47.7	75	12.0	+ 6.0	59.8
5	Amigen	126.0	5.0	62.9	78	14.1	+ 3.1	59.5
6	Egg	..	87.9	40.6	73	11.1	-10.3	58.6

not approached until the second period when the caloric intake improved. The patient recovered temporarily to die a year later of the malignant disease.

The observations of Table 6¹⁰ comprise an almost perfect human metabolism study previously reported in detail. For 85 days, Periods 2 to 18, amino acids afforded the chief nitrogen intake except for 5 days with Amigen. During 70 of the 85 days the nitrogen was given parenterally. The

ous mixtures in Period 2. This mixture Vuj appears not so well tolerated¹² as some others studied.¹⁵ The utilization of Amigen and Vuj in Periods 3 and 4 respectively was quite comparable. The similar quantities of undetermined nitrogen for these 2 periods should be noted in view of the discussion above. The undetermined nitrogen was much less when natural protein was given in Periods 1, 19 and 20. It did not decline significantly when

the amino acids were given orally in Periods 12 to 14 but the urea and ammonia fraction dropped sharply. Nitrogen balance became strongly positive.

Histidine omission in Periods 16 and 17, Table 6, caused a rise in urinary nitrogen and negative balance. It appears that histidine may be required by this patient with chronic ulcerative colitis. Both histidine and arginine may apparently be omitted from the intake of normal man in nitrogen equilibrium.²³

Orally the amino acid mixture and Amigen were rather similarly utilized *in toto* although the proportions were different in the data of Table 7.¹⁰ This same patient as studied in Table 6 did not obtain the same clinical improvement from the oral administration of both the amino acids and the basal diet as he did from the parenteral feeding of Table 6. The amino acids were more palatable and associated with a lower fecal nitrogen than the Amigen, but the urinary total nitrogen and the undetermined fraction were higher. When whole egg replaced the Amigen the urine nitrogen fractions dropped conspicuously.

Discussion. The above observations and comment concern the use of complete mixtures of amino acids for general nutrition. Single or several amino acids in groups may find a practical place in the supplementation of diet protein. Other more specific uses may be discovered. As a single amino acid, *methionine* has already found a place in clinical therapy³ following demonstration experimentally of its detoxifying action.^{7,18}

Synthetic amino acid mixtures permit obvious flexibility not possible with protein digests. It is not unreasonable to suspect that injury of a specific tissue might be most rapidly repaired by a mixture of amino acids corresponding to that tissue. We believe, however, that most tissue proteins are constructed from plasma proteins by more or less modification of plasma protein molecules, sometimes probably with addition or subtraction of amino acids. If this be true then the amino acid

constituents of these plasma proteins might dictate the basic make-up of the amino acid mixture to be given the patient. If, for example, one would enhance the production of protective globulins a knowledge of the make-up of the gamma globulins might determine the best admixture of amino acids for that specific purpose. For other specific purposes, other admixtures might be indicated and would be permitted by use of synthetic mixtures.

The amino acid mixtures are better tolerated parenterally and more palatable orally than various protein digests tested in this laboratory. On the other hand the practical problems and the economics of large scale production of pure amino acids will have much to do with determining the extent of use of such materials.

The importance of adequate protein nutrition for all patients appears obvious to most of us, but too often obvious needs are neglected. As a single item in the treatment of all patients we believe that adequate protein nutrition cannot be surpassed in importance. Some day physicians should have within easy reach the necessary materials for maintaining protein nutrition in the sick or injured patient where effective parenteral administration is a necessity—a prospect for the near future.

Summary. Amino acids can supply the protein nitrogen requirements of the body. The so-called 10 essential amino acids in suitable amounts can be given by mouth, by vein, subcutaneously or intraperitoneally with equal success in maintaining nitrogen and weight equilibrium.

These 10 essential amino acids are threonine, valine, leucine, isoleucine, lysine, tryptophane, phenylalanine, methionine, histidine and arginine. Glycine is usually added to this mixture.

By mouth the amino acids are utilized a little more completely than when given parenterally. Our experiments give no evidence that the unnatural isomers of the amino acids are toxic and some are probably used in the body.

These amino acid mixtures can be given

rapidly in 10% solution parenterally and cause less clinical disturbance than any protein digests so far tested. Glutamic acid in digests or amino acid mixtures is not well tolerated by vein and may induce vomiting.

Abundant production of plasma proteins in standardized dogs is readily demonstrated as due to these amino acids as the sole source of nitrogen. The production of new plasma protein due to

amino acids in general corresponds favorably with the response to high grade diet protein in equivalent amounts.

Our first observations were upon dogs but subsequent observations on human patients gave the same picture.

These amino acid mixtures are well utilized by patients suffering from chronic infection (colitis), gastro-intestinal disturbances (partial obstruction) or cancer cachexia.

REFERENCES

1. ALBANESE, A. A.: *Bull. Johns Hopkins Hosp.*, **75**, 175, 1944.
2. BASSETT, S. H., WOODS, R. R., SHULL, F. W., and MADDEN, S. C.: *New England J. Med.*, **230**, 106, 1944.
3. BEATTIE, J., and MARSHALL, J.: *Nature*, **153**, 525, 1944.
4. DAFT, F. S., ROBSCHT-ROBBINS, F. S., and WHIPPLE, G. H.: *J. Biol. Chem.*, **123**, 87, 1938.
5. EARLE, D. P., SMULL, K., and VICTOR, J.: *J. Exp. Med.*, **76**, 317, 1942.
6. FINK, R. M., ENNS, T., KIMBALL, C. P., SILBERSTEIN, H. E., BAILE, W. F., MADDEN, S. C., and WHIPPLE, G. H.: *J. Exp. Med.*, **80**, 455, 1944.
7. GOODELL, J. P. B., HANSON, P. C., and HAWKINS, W. B.: *J. Exp. Med.*, **79**, 625, 1944.
8. HOLMAN, R. L., MAHONEY, E. B., and WHIPPLE, G. H.: *J. Exp. Med.*, **59**, 251, 1934.
9. MADDEN, S. C., ANDERSON, F. W., DONOVAN, J. C., and WHIPPLE, G. H.: *J. Exp. Med.*, 1945 (in press).
10. MADDEN, S. C., BASSETT, S. H., REMINGTON, J. H., MARTIN, F. J. C., WOODS, R. R., and SHULL, F. W. (in press).
11. MADDEN, S. C., CARTER, J. R., KATTUS, A. A., JR., MILLER, L. L., and WHIPPLE, G. H.: *J. Exp. Med.*, **77**, 277, 1943.
12. MADDEN, S. C., and CLAY, W. A.: *J. Exp. Med.*, **82**, 65, 1945.
13. MADDEN, S. C., KATTUS, A. A., JR., CARTER, J. R., MILLER, L. L., and WHIPPLE, G. H.: *J. Exp. Med.*, 1945 (in press).
14. MADDEN, S. C., and WHIPPLE, G. H.: *Physiol. Rev.*, **20**, 194, 1940.
15. MADDEN, S. C., WOODS, R. R., and SHULL, F. W.: *J. Exp. Med.*, **81**, 439, 1945.
16. MADDEN, S. C., WOODS, R. R., SHULL, F. W., and WHIPPLE, G. H.: *J. Exp. Med.*, **79**, 607, 1944.
17. MADDEN, S. C., ZELDIS, L. J., HENGERER, A. D., MILLER, L. L., ROWE, A. P., TURNER, A. P., and WHIPPLE, G. H.: *J. Exp. Med.*, **73**, 727, 1941.
18. MILLER, L. L., ROSS, J. F., and WHIPPLE, G. H.: *Am. J. Med. Sci.*, **200**, 739, 1940.
19. RATNER, S., SCHOENHEIMER, R., and RITTENBERG, D.: *J. Biol. Chem.*, **134**, 653, 1940.
20. RATNER, S., WEISSMAN, N., and SCHOENHEIMER, R.: *J. Biol. Chem.*, **147**, 549, 1943.
21. ROSE, W. C.: *Physiol. Rev.*, **18**, 109, 1938.
22. ROSE, W. C.: Unpublished observations.
23. ROSE, W. C., HAINES, W. J., and JOHNSON, J. E.: *J. Biol. Chem.*, **146**, 683, 1943.
24. TOTTER, J. R., and BERG, C. P.: *J. Biol. Chem.*, **127**, 375, 1939.

THE EFFECT OF SALICYLATE THERAPY ON THE WELTMANN SERUM COAGULATION REACTION AND ITS USE AS A PROGNOSTIC TEST IN RHEUMATIC FEVER*

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An objective laboratory test which can measure the activity of a disease process and aid in the evaluation of prognosis is constantly being sought. For a long time the clinical course of the patient with an infectious disease has been compared with the temperature, and total and differential white blood cell counts; more recently serial determinations of the sedimentation rate of erythrocytes have been widely used. Weltman's discovery that serum is coagulated by solutions of calcium chloride has provided another useful test.⁹

Chemotherapeutic agents alter the clinical course of infectious diseases by controlling growth of the etiologic agent or by abolishing symptoms of the disease. In the latter case a false sense of security regarding the arrest of the pathologic process may arise. The introduction by Coburn of massive salicylate therapy for controlling the clinical manifestations of rheumatic fever and suppressing the inflammatory process has created the need for a prognostic laboratory test which is unaltered by salicylates.² The rationale of salicylate therapy in relation to antigen-antibody reactions and hypersensitivity in rheumatic fever has recently been reviewed by Aikawa.¹ The sedimentation rate has been the most widely used laboratory aid for the determination of rheumatic activity but it has been shown to be altered *in vitro* by the presence of salicylates.⁵ Concentrations necessary to depress the sedimentation rate can be achieved *in vivo* by massive salicylate therapy.

The Weltmann reaction has been shown

to be equal or superior to the sedimentation rate as a prognostic aid in rheumatic fever.⁷ Since the sedimentation rate is affected by salicylate therapy, the Weltmann reaction, if it is not affected by salicylates, should be a superior test. The effect of salicylates on the Weltmann reaction was studied *in vitro*. After alteration in the coagulation band was found only with high concentrations of salicylates, the Weltmann coagulation reaction in the presence of various blood levels of salicylate was compared *in vivo* with the sedimentation rate, and the total white blood cell count.

Material and Methods. *In vitro studies:* Sodium salicylate was dissolved in normal human serum to make a 1% solution. Weltmann coagulation bands were determined on samples of serum from 4 normal individuals. Aliquots of these samples were diluted with the stock salicylated serum, so that the final concentrations were 200, 400, 600, 800, 1000, 2000 and 6000 γ per cc. of serum. These levels approximate those found in the blood of patients receiving salicylate therapy.

In vivo studies: Over a period of 6 months, 86 Weltmann coagulation tests were done on 26 rheumatic patients on the wards or in the Out-Patient Clinic of the North Carolina Baptist Hospital. The clinical diagnoses in this group are shown in Table 1.

The total white blood cell counts, sedimentation rates, and blood salicylate levels of these patients were also followed, but only those determinations done on the same day as the Weltmann test are considered in the analysis of data.

* Presented at the meeting of the Southern Section of the American Federation for Clinical Research, Atlanta, Georgia, December 8, 1945.

Wetmann reaction: A stock solution of 10% calcium chloride hexahydrate ($\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$) was prepared; this compound was used, as has been suggested by Schweinburg and Evans, in order to keep the pH in the favorable range of 7.2 to 7.8.⁸ From the 10% solution 10 stock dilutions were made, containing in arithmetic progression 0.1 to 0.01% calcium chloride. The tests were run by shaking 5 cc. of each calcium chloride dilution with 0.1 cc. of non-hemolyzed serum in small test tubes arranged in a rack. The rack was left in a boiling water bath for 15 minutes and the reaction was then read. On each series of tests two control tests with normal serum were run simultaneously; the coagulation bands on the normal sera were always 6.

Figure 1 is a scatter chart of the results. The salicylate levels varied from 0 to 1073 γ per cc.; the coagulation band usually fell below 6, since rheumatic diseases in the acute stage are characterized by inflammation. An analysis of co-variation of these data (Table 2) failed to reveal any significant degree of correlation between the two determinations, either between the means of tests on the 27 patients or within series of tests on the same patient. Both of these correlations are statistically non-significant and may therefore be attributed to chance variations.*

Wetmann tests were done on additional hospitalized patients who were receiving

TABLE 1.—DISTRIBUTION OF CASES

Clinical Diagnosis	Number of cases
Rheumatic fever:	
Active rheumatic fever without demonstrable heart disease	8
Active rheumatic fever with heart disease	3
Rheumatic chorea without demonstrable heart disease	2
Inactive rheumatic heart disease, bacterial endocarditis	1
	— 14
Atrophic arthritis	10
Erythema nodosum	1
Hypertrophic arthritis	1
	—
Total	26

Sedimentation rate: Five cc. of venous blood was collected in specially prepared bottles containing 4 mg. of potassium and 6 mg. of ammonium oxalate. The oxalated blood was placed in Wintrobe tubes and the observed values were corrected according to the method of Wintrobe and Landsberg.¹⁰

Blood and salicylate levels: Salicylate levels were determined on fasting venous blood according to the method of Coburn.²

Results. *In vitro* studies: The coagulation band was found to be unchanged by the addition of 200 to 800 γ of sodium salicylate per cc. The addition of 1000 to 6000 γ per cc. increased the coagulation band from 6 to 7; such levels would rarely be achieved in patients and would be accompanied by symptoms of salicylism.

***In vivo* studies: Blood salicylate levels:** A total of 86 determinations of the blood salicylate levels were made on the same day that the Wetmann test was done.

salicylate therapy for various conditions unrelated to the rheumatic state. The data are not included in this report, but the results closely parallel those in the rheumatic group.

Sedimentation rate: Sixty Wetmann tests were done on the same day that the sedimentation rate was determined. Figure 2 is a scatter chart of the results. The mean line has a negative slope, indicating that in general the higher the sedimentation rate, the lower the coagulation band will be. As the sedimentation rate decreases toward normal, the coagulation band approaches a normal value of 6.

White blood cell count: In 19 cases 44 Wetmann reactions were determined on the same day that a white blood cell count was made. Figure 3 shows a scatter chart of these data. The mean line has a negative slope, indicating that in general the

* A statistical analysis of these two sets of data was made by Dr. Charles W. Cotterman.

TABLE 2.—ANALYSIS OF CO-VARIATION OF BLOOD SALICYLATE LEVEL AND WELTMANN REACTION

Source of co-variation	Degrees of freedom	Correlation coefficient
Between means of patients	25	-0.131 (non-significant)
Within patients	56	+0.070 (non-significant)
Total	84	-0.026 (non-significant)

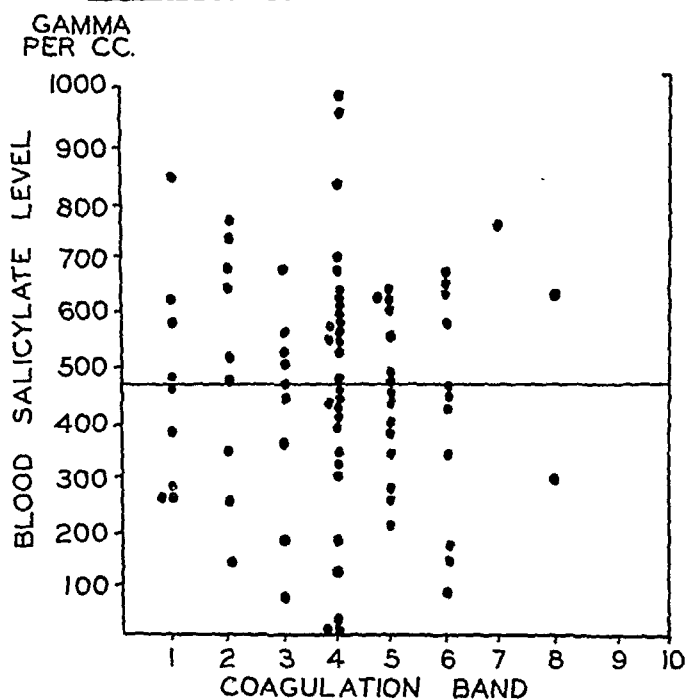


FIG. 1.—Weltmann reaction compared with blood salicylate level in 26 rheumatic patients.

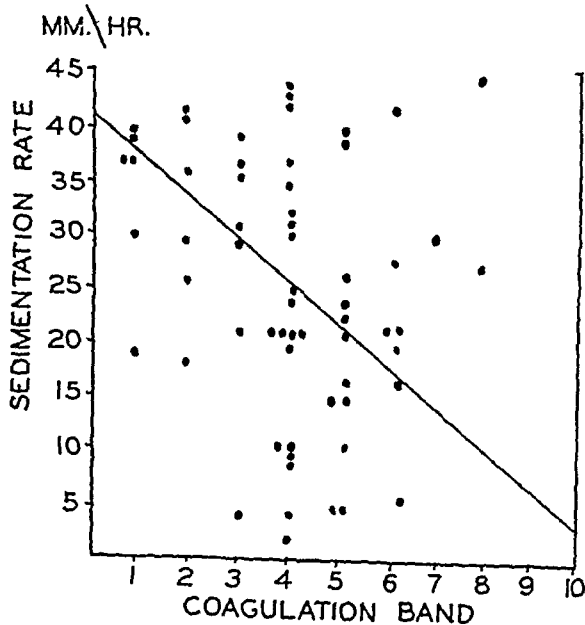


FIG. 2.—Weltmann reaction compared with corrected sedimentation rate in 22 rheumatic patients receiving salicylates.

higher the white blood cell count, the lower the coagulation band will be.

Discussion. *Weltmann reaction as a prognostic aid in rheumatic fever:* The factor of greatest importance in determining the prognosis of rheumatic fever is the presence or absence of active inflammation, with damage to the heart. In exudative reactions, which are associated with acute infection, the coagulation band is usually shifted to the left. This shift is paralleled by an elevation of the sedimentation rate and white blood cell count.⁷ If the myo-

activity the patient should be allowed. Comparisons of the Weltmann reaction and the sedimentation rate in rheumatic fever and other processes—such as tuberculosis—which show similar progression from exudation to fibrosis have shown that the coagulation band does not always correspond to the sedimentation rate, but appears to reflect more accurately the anatomic pathologic change.⁴

Comparison of the Weltmann reaction and the sedimentation rate in the presence of salicylates: The relationship between the

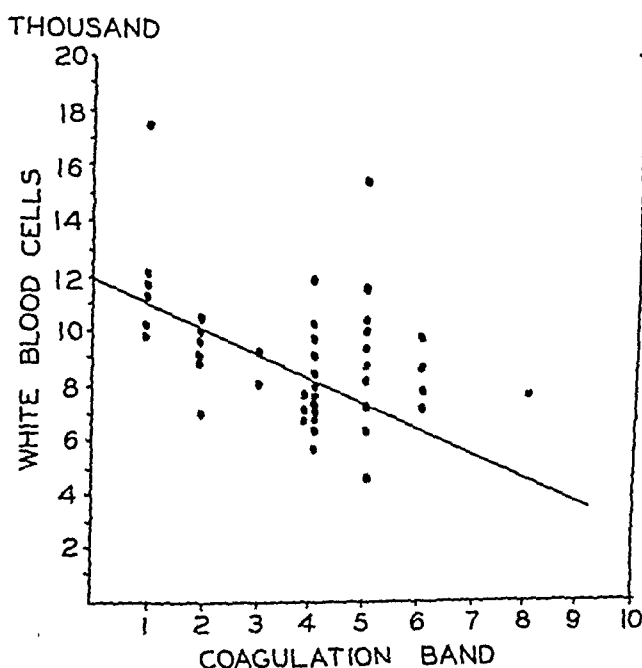


FIG. 3.—Weltmann reaction compared with white blood cells in 19 rheumatic patients receiving salicylates.

cardium is involved in the inflammatory or exudative process, the electrocardiogram may show an alteration of the PR interval and complexes; this test gives no information on the state of the valves.

The development of fibrosis is accompanied by a shift to the right in the coagulation band and is part of the healing process which may cause distortion of the heart valves by excessive scarring. The detection of this process before the development of audible murmurs would be of great aid in determining the amount of

Weltmann reaction and the corrected sedimentation rate in patients with rheumatic fever has been shown by other investigators to be roughly parallel.⁷ These studies were done before the introduction of massive salicylate therapy by Coburn, and it is not clear whether any salicylates were administered to the patients during these previous studies.

The mechanism of the Weltmann coagulation reaction is not well understood. It is thought to be a physico-chemical change in the state of the serum proteins initiated

by the addition of calcium ions. It should be noted that the Weltmann test is performed with serum and the sedimentation rate determination with plasma; no extraneous ions are introduced in the collection of specimens for the Weltmann reaction. The sedimentation rate has been found to parallel closely the level of plasma fibrinogen, a substance thought to be formed in the liver;³ the chemical relationship of salicylates to dicumarol has recently been pointed out, and dicumarol has been shown to depress plasma prothrombin by the effect on the liver.⁶ Hence, the sedimentation rate may be artificially altered by the effect of salicylates on the production of fibrinogen as well as by the effect on the disease process.

Lichty and Hooker conclude that a salicyl compound administered to patients as acetylsalicylic acid may have the ability to lower the sedimentation rate artificially.⁵ They quote studies of Bendien, Newberg and Snapper, who noted that when sodium salicylate is added to human blood *in vitro*, the erythrocyte sedimentation rate is greatly reduced. Preliminary experiments of the former authors indicated that the minimal concentration of sodium salicylate necessary to depress the sedimentation rate *in vitro* was 90 to 120 mg. per 100 cc. (900 to 1200 γ per cc.*); our *in vitro* studies indicate the Weltmann reaction is altered only slightly at this range. In patients the marked drop in the sedimentation rate noted after the institution of acetyl salicylic acid therapy in ordinary doses is reversed by withdrawal of the drug. The variation in the sedimentation rate is far greater in proportion than is that in the Weltmann coagulation band noted in the present report. Both the *in vitro* and the *in vivo* data seem to indicate that the Weltmann reaction is relatively less altered by even high levels of salicylate than is the sedimentation rate. Hence, it should be superior as a prognostic aid.

Comparison of the Weltmann reaction and the white blood cell count: The white blood cell count has been used as a measure of tissue destruction in non-infectious processes—such as myocardial infarction—as well as in infectious processes. The data in Figure 3 indicate that there is a rough parallel between the white blood cell count and the coagulation band. It has been shown that extraneous factors, such as the time of day and the relation to meals, have a marked effect on the white blood cell count. These factors do not alter the Weltmann coagulation band.

Summary. 1. Serial studies of the Weltmann coagulation reaction, the corrected sedimentation rate, and the white blood cell count were made over a period of 6 months in 26 patients with rheumatic states who were receiving salicylate therapy.

2. The Weltmann coagulation reaction was found to be unaltered *in vitro* or *in vivo* by levels of salicylates commonly attained in the blood.

3. Even in the presence of salicylate therapy a low Weltmann coagulation band, an elevated sedimentation rate, and an elevated white blood cell count are all indications of an inflammatory process. The coagulation band is least affected by extraneous factors, however, and gives the most uniform results.

4. The Weltmann coagulation band agreed more closely with the clinical course and symptoms in patients studied than did the sedimentation rate or white blood cell count.

5. The Weltmann coagulation reaction seems to be a better measure of activity and a more accurate index to the prognosis of rheumatic fever in patients receiving salicylate therapy than other laboratory aids now available.

* Since the paper was submitted for publication, Homburger has published in this Journal (AM. J. MED. SCI., 210, 165, 1945) *in vitro* studies which clearly show depression of the sedimentation rate by concentrations of as little as 30 mg. of sodium salicylate per 100 cc. of plasma, if the plasma is allowed to stand for 24 hours before the test is run.

REFERENCES

1. AIKAWA, J. K.: *Ann. Int. Med.*, **23**, 969, 1945.
2. COBURN, A. F.: *Bull. Johns Hopkins Hosp.*, **73**, 435, 1943.
3. ERNSTENE, A. C.: *AM. J. MED. SCI.*, **180**, 12, 1930.
4. LEVINSON, S. A., and KLEIN, R. I.: *Am. Rev. Tuberc.*, **37**, 200, 1938.
5. LIGHTY, J. A., and HOOKER, S. P.: *Proc. Soc. Exp. Biol. and Med.*, **48**, 69, 1941.
6. QUICK, A. J.: *Physiol. Rev.*, **24**, 297, 1944.
7. SCHERLIS, S., and LEVY, D. S.: *Am. Heart J.*, **26**, 355, 1943.
8. SCHWEINBURG, F. B., and EVANS, L. R.: *J. Lab. and Clin. Med.*, **27**, 366, 1941.
9. WELTMANN, O.: *Med. Klin.*, **26**, 240, 1930.
10. WINTROBE, M. M., and LANDSBERG, J. W.: *AM. J. MED. SCI.*, **189**, 102, 1935.

PSITTACOSIS TREATED WITH SULFONAMIDE DRUGS

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FIVE patients ill with psittacosis were admitted to the Department of Contagious Diseases, Cleveland City Hospital during January 1942. Two others exposed to infected parrakeets in the same pet shop were admitted to another hospital; one of these died. The ages of the patients in City Hospital were 34, 36, 37, 44 and 71 years; 2 were females and 3 were males.

The most common symptoms were extreme malaise, weakness, chills and fever. Others were headache, constipation, myalgia and a cough which in 2 patients was dry, irritative and essentially non-productive.

Roentgen examination of the lungs showed pneumonia to be present in all patients, the character of which was consistent with the diagnosis of psittacosis bronchopneumonia. It cleared on an average of 19.4 days, the least number of days being 15 and the greatest 25.

In Patients 1 and 4 (Table 1) there was a drop in the temperature curves after sulfonamide drugs had been administered. Clinically, however, they remained extremely ill, having general malaise and weakness for a long time. Neither was benefited. Patient 5 was not very ill and his constitutional symptoms disappeared soon after admission. Neither sulfapyridine nor sulfathiazole brought down his temperature.

Patients 2 and 3 were seriously ill on admission and sulfapyridine had no effect on the clinical course; if anything the patients seemed worse. The extreme malaise in these 2 patients was still present on the 27th and 31st hospital days, respectively, the days when they were discharged from the hospital.

Patient 3 was probably the most acutely

ill of all the patients. She was a typical case, a direct exposure, and yet she did not have a positive complement-fixation test nor did she respond to sulfonamide drugs.

In Patient 4 the temperature became normal within 24 hours after admission, but it took almost 2 weeks before the lungs became clear.

Of the 5 patients treated with sulfonamide drugs, Patient 1 was the only one that might have been said to have responded somewhat to a sulfonamide in that the temperature became normal within 2 days after treatment started. On the other hand, the patient still had pathologic findings in the lungs which did not clear until approximately the 20th hospital day. It may be that some of the other sulfonamide drugs might have given other results, but certainly it can be said that neither sulfapyridine nor sulfathiazole was the drug of choice in treating this infection. This is the experience of others. Heilman *et al.* advised penicillin in large doses in the comparable disease of ornithosis.¹ Our own clinical guess is that even penicillin would be of little value.

The owner of the store (M. K.) who housed the infected parrakeets, was admitted to another hospital and died from the disease. The blood serum of his wife who had not been hospitalized fixed antigen in a dilution of 1:32 (4+). The complement-fixation test is reliable. However, one has to differentiate psittacosis from lymphogranuloma venereum, since the blood serums of patients ill with the latter disease also react to psittacosis antigens.² There was no evidence of this disease in our patients.

Parrakeets were collected from the

TABLE 1.—CLINICAL DATA ON 5 PSITTACOSIS CASES

	1	2	3	4	5
	<i>F. W. No. 239951</i>	<i>G. F. No. 239953</i>	<i>N. B. No. 239955</i>	<i>I. K. No. 240063</i>	<i>M. G. No. 240183</i>
Age	36	37	34	44	71
Sex	M	F	F	M	M
Color	W	W	W	W	W
History of contact	Worked in store, and tended cage	Worked in store, and handled birds	Worked in store, and handled birds	Helped in pet shop where sick parrot died; bitten by parakeet	Was given pair of love birds
Symptoms on admission . .	Weakness, malaise, myalgia, chills, headache, fever	Weakness, malaise, fever, constipation, nausea and vomiting, anorexia, cough	Weakness, myalgia, fever, constipation, cough	Weakness, malaise, chills, fever, cough, constipation	Fever, drowsiness, chills and headache
No. days ill before admission .	7	8	5	9	3
Chest film on admission . .	Pneumonia in lower half of left lung field	Pneumonia in lower portion of left lower lobe	Pneumonia in lower half of right lung field	Pneumonia in middle third of left lung field extending toward apex	Negative on admission
Subsequent Roentgen ray examination of chest	11 days later almost complete clearing 17 days later nearly clear; clear on 20th hospital day (H.D.)	14 days later slight clearing Lungs clear 22 days later	14 days later clear	7 days later almost clear 13 days later clear	Pneumonia in right apex and subapical area 8 days later Almost clear 20 days later
Hospital course	Sulfapyridine, total of 21 gm. for 6 days Temp. 39°-39.7° C.; normal in 2 days; discharged on 22nd H.D.	Sulfapyridine, total of 16 gm. for 4 days; sulfathiazole, total of 30.5 gm. from 8th to 12th H.D. Temp. 38° C.; on sulfapyridine it rose to 39° C.; sulfathiazole 8th H.D.; temp. normal on 13th H.D.; vomited, malaise; marked cough present on discharge Negative	Sulfapyridine, total of 27 gm. for 8 days; sulfathiazole, total of 31 gm. from 8th to 13th H.D. Cough for approximately 19 days; temp. 38°-40.8° C.; av. 39° C. for 13 days; normal on 14th H.D.; marked malaise	Sulfapyridine, total of 29.5 gm. for 5 days Temp. on admission 39.5° C.; normal in 24 hrs. and thereafter; in spite of normal temp., patient had malaise up until 6th H.D.	Sulfapyridine, total of 19.5 gm. for 4 days; sulfathiazole, total of 7 gm. from 3th to 7th H.D. Symptoms cleared soon after admission; hicoughs 9th to 13th H.D.; temp. 38.7° C. on admission; went up to 40° C. on 2nd H.D.; av. 39° C. for 6 days; 38° C. 7th and 8th days; normal thereafter Not done
Blood culture	Negative	9.6	5.7	8.5	12.0
White blood count	5.7	69% polymorphonuclears 1/64-4+	80% polymorphonuclears (-)	55% polymorphonuclears Bottle broke	69% polymorphonuclears Not done
Complement fixation . . .	1/128-4+				

wholesale dealer who supplied birds to the storekeeper previously mentioned as well as to Patient 5 (M. G., the owner of 2 parakeets). Eleven birds with different code numbers were sacrificed and sent to Dr. Karl F. Meyer of the George Williams Hooper Foundation. Psittacosis virus was recovered from 6 birds. Harlin L. Wynns, Chief of Bureau of Epidemiology of California commented as follows:

"Since six different code numbers were positive, we cannot help but believe that these birds were infected on the premises of the dealer, and we are rather discouraged because of all the states raising and selling shell parakeets in interstate traffic, we are the only one doing routine systematic testing and permit shipment only of stock tested and found free of infection.

"The shell parakeet is found infected in its native habitats. Therefore, it is safe to assume that the original importations of such birds into the United States contained infected stock. Furthermore, it is highly improbable that birds raised in

states other than California are free of infection.

"We test our stock regularly and destroy all aviaries found infected. The aviaries breeding the birds shipped to Cleveland were all laboratory tested within the past year and found free of infection. Our percentage of aviaries found infected during last year's testing was very low (less than 5%), and these were destroyed completely under supervision. We feel that until laboratory testing is required of all shell parakeet breeding aviaries in the United States, such problems will continue to arise."

In all probability the infection was introduced from sources other than California and birds from the latter state subsequently became infected here.

Summary. Five patients ill with psittacosis were treated with sulfapyridine and some with sulfathiazole as well. It could not be stated that the patients were benefited by the use of either drug.

We are grateful to Dr. K. F. Meyer of the George Williams Hooper Foundation in San Francisco who ran the psittacosis complement-fixation tests and directed that the parakeets collected by our Health Department be tested for the presence of the virus.

REFERENCES

1. HEILMAN, F. R., and HERRELL, W. E.: Penicillin in the Treatment of Experimental Ornithosis, *Proc. Staff Meet., Mayo Clin.*, **19**, 57, 1944.
2. RAKE, G., EATON, M. D., and SHAFFER, M. F.: Similarity and Possible Relationship Among Viruses of Meningo-pneumonitis, Lymphogranuloma Venereum and Psittacosis, *Proc. Soc. Exp. Biol. and Med.*, **48**, 528, 1941.

THROMBOPHLEBITIS WITH MULTIPLE PULMONARY EMBOLI

PSYCHIATRIC SELF-OBSERVATIONS

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THE method of introspection has much against it. In the first place, the number of cases is restricted to one, if the observer is the same. In the second place, there are many sources of error. We all have a certain image of ourselves, and what does not fit into that picture we may overlook in any introspective efforts. For example, one may not want to admit that one is afraid and so may overlook the many disguises of fear. This source of error is even greater if one wishes to communicate the results of one's introspection to others. There is also the complicated problem of amnesia: some things that seem to be genuinely forgotten may be recalled very clearly when—as the lawyers put it—one's memory is "refreshed." All these sources of error are particularly great when the borderline of the abnormal is reached. Yet no one can deny that certain psychologic phenomena are open only to the introspective method.

I have decided to set down certain mental experiences that I had during a recent very severe illness. The background for my interest in this psychosomatic study is a great deal of work as psychiatric consultant in general hospitals. In such work I have found how important it is that certain psychopathologic syndromes in physical disease be diagnosed very early. It is sometimes difficult in severe cases of physical illness or in post-operative cases to distinguish minor transitory mental symptoms from beginning stages of more serious syndromes, such as depression or delirium. But from the point of view of prompt and proper therapeutic steps it is very important. I believe my own introspective experiences during the course of a severe physical disease are significant for the practicing physician and also have some importance for the theory of psychopathology.

Some of these experiences of mine, which I would classify as distinctly abnormal, have never been described from inside. The so-called phenomenologic school of psychopathology promised us such studies in general and theoretical articles, but has actually furnished little that is valid or practical.

I developed a thrombophlebitis in the right leg without known cause and during a period of excellent health and activity following a vacation. Under the treatment of a private physician I followed a course of complete bed-rest for about 3 weeks. Then what was evidently a small pulmonary embolus was followed within a week by further pulmonary emboli. Altogether there were probably 3 or 4. I developed a high temperature, took sulfa drugs, lost all appetite, became very toxic. When taken to the hospital I was in a very critical condition. Within a few hours after reaching the hospital I had an emergency operation, a ligation of the right femoral vein. The same night a course of penicillin was begun. Owing to the fact that the thrombus extended very high and that there was an anomaly in the location of the blood-vessels, which were deeper than usual and differently placed, the operation was more difficult and lasted longer than usual. It was carried out under local anesthesia, preceded by scopolamine, $\frac{1}{150}$ gr., and morphia, $\frac{1}{8}$ gr.

I deliberately refrain from giving surgical or medical details of my case history. They are not pertinent to the points I want to make here. The emphasis of the discussion of the first operation and a few days following it is more on the qualitative aspects, and less on the causative aspects, of the mental state. It would be difficult to isolate the causes exactly. There were present high fever, a general

toxic condition, scopolamine. It is important to emphasize that emotional factors played no part—or an insignificant one—in this condition.*

My experiences confirm the generally known psychologic law that one is apt to forget unpleasant experiences and remember pleasant ones. Two factors have become clear to me with regard to this amnesia. In the first place, pleasant or indifferent experiences are, of course, forgotten, too, in such circumstances of severe physical disease. Secondly, there are two types or kinds of amnesia: forgotten experiences that cannot be recalled even when one's memory is refreshed and those that are recalled easily. I have been told of some more or less indifferent things which I said that I have completely forgotten. I have been told of others which I seemed to have forgotten but which then I immediately recalled.

For long periods of time during the first operation I was in a state of sleep, or at any rate without full consciousness. At other times I was fully awake and clear. My main concern was with pain. It seems to me extraordinary how much I have forgotten about this pain (now, many weeks later). But I have not only a distinct memory of a memory of the pain, I have also notes to go by, notes which I dictated soon after I got a little better.

When I had this pain during the operation it filled my whole mind. There was literally no room for anything else. It is difficult to verbalize these pain experiences. For considerable periods when I was clear there would be no pain at all. Then suddenly it would come. On account of the danger of further emboli, spinal anesthesia was contraindicated. As

I understand it, the deeper structures are less accessible to local anesthetics, and certain types of pain, like that of actual ligation, are not susceptible to complete anesthesia at all.

It is hard to describe one's emotional reaction to pain. It is partly a fear of more pain to come, of its continuing or getting worse; partly a hope that pain will cease (which, of course, it often did) or lessen, the "*speranza di minor pena*" Dante wrote about. Of this, more later.

During the first operation my attention was focused on concern with my body. Freud made a well-known statement about the distribution of "libidinal interest" in physical illness: "It is universally known and seems to us a matter of course, that a person suffering organic pain and discomfort relinquishes his interest in the things of the outside world, insofar as they do not concern his suffering. Closer observation teaches us that at the same time he withdraws libidinal interest from his love-objects: so long as he suffers, he ceases to love. . . . The sick man withdraws his libido back upon his own ego, and sends it forth again when he recovers."²

It is true, according to my recollection, that my libido certainly was withdrawn to my body and my interest in the outside world was decidedly restricted to what had direct bearing on my immediate situation. But in the midst of the operation, during a period when I was either anticipating pain or enduring it, I asked one of the physicians standing near me to find my wife downstairs and tell her everything was going fine. This preoccupation must have been very strong because after this physician had carried out my request and told me about it, I sometime afterward

* This statement requires some explanation: before the operation, when one embolus followed the other, during the operation and immediately after it, I was in danger of death. As a physician I should have known that merely from the objective medical symptoms, which I understood intellectually. It should have been even clearer to me when the director of the surgical service came from some distance to do the operation at once as an emergency on a Sunday afternoon, and when the head of a medical service also came on a Sunday afternoon, to see me at once. Moreover, I remember the serious faces of some of my medical friends who were there at the time. But I interpreted their concern as sympathy with the pain the emboli were causing, and at no time before, during or within a few days after the first operation did the idea even remotely enter my consciousness that I was in danger of dying, as I now know I definitely was. One might interpret this as a sort of protective mental amblyopia.

asked him the same thing again. This would indicate, in the light of my experience, that Freud's formulation is an oversimplification of very complicated levels and processes of emotional thinking.

During the periods when I was conscious and there was no pain, my intellectual capacities were greatly reduced. Some medical friends were standing near me during the operation (I was separated by a screen from the operating surgeon). On a number of occasions they talked to me in an effort to cheer and encourage me. Most of what they said was away over my head. I simply did not understand what they meant, though I heard their voices very clearly and was aware of their words, the finer modulations of their voices and their friendly intent.

The contrast between my keen awareness of the modulation of voices and my lack of intellectual understanding of what the voices said astonishes me now. At that time, however, the fact that I did not understand most of what was said to me caused me neither surprise nor anxiety. It seemed to me self-understood. For example, one doctor remarked to me—and I recognized the friendly, humorous tone—"Just like a psychiatrist, you are constituted peculiarly." (He was referring to the anomaly in location of the blood-vessels which caused prolongation of the operation.) Ordinarily this is the type of joke I would enjoy; but I understood then neither the joke nor the meaning of the sentence. Yet I took it for granted that I could not understand and asked no question. It was as if I were a child or an infant among grown-ups.

Mannheim, an author who made experiments with scopolamine upon himself, mentions among other things, "deterioration of comprehension and of intellectual performance."³ My experiences throw a clearer light on the nature of this disorder of comprehension. Toward the latter part of the operation the anesthetist removed the gauze that was over my face, because she felt I was getting too warm. As I looked sideways I saw a large clock

on the wall. I remember distinctly what was in my mind. I thought the operation was lasting very long and I was fervently hoping it would be over soon. I thought I would read the time on the clock, figure out at what time I went up to the operating room, and then I could figure out about when the whole thing would be over.

When I looked at the clock, I saw numbers in a circle. I recall particularly the 6 and the 7. I said to myself that the position of the numbers on the clock—at the top, the bottom or the side—had a meaning for telling time. But I could not figure out how. I remembered that each number meant something. But I was not sure how one picked a special number. I do not know whether or not I saw the clock's hands. At any rate, I did not comprehend that they pointed to the numbers. According to my memory, I spent considerable time trying to make out this clock. What surprises me now is how indifferent I was at my inability to solve it. I have no recollection of any anxiety in connection with this lack of comprehension. My attitude was: This is the sort of thing well people know about, and it is quite natural that I do not.

Neither did it occur to me that the whole problem I was working on was meaningless, since I had no idea of what time it was when I had been taken to the operating room, and since I had no way of knowing anyhow how long the operation⁴ would continue.

Diagnostically, my inability to read the clock was a form of agnosia. Agnosia is a symptom which we know best from organic lesions in the occipital lobe, such as occur frequently, for instance, in carbon monoxide poisoning.² I could recognize the object, know its name, differentiate its details, but could not apperceive it as a whole nor make use of its function. I conclude from this that definite disorders of the higher processes of perception such as agnosia may be a component of the disorder of comprehension in scopolamine intoxication.

I remember only two factors which

alleviated my general feeling of insecurity while on the operating table. One was the voice of the operating surgeon and one was the reassurance derived from definite physical contact.

The surgeon's voice was deep, calm and authoritative. It was not raised at any time. One episode was characteristic of my mental state. I developed a very disagreeable pain in the right calf during the operative procedure. Somehow it seemed to me that this was due to my leg "falling asleep," as if it were in an awkward, hanging position from the knee down. (Not true, of course.) I remember that several times I moved the leg, seeking to ease its position—not exactly an appropriate behavior in the situation. I recall very distinctly the surgeon's voice saying quietly but definitely: "Don't move your leg, Dr. Wertham." My emotional response to this remark is difficult to describe. From that moment on, it was unthinkable that I should move my leg, however it felt. The remark had such an authoritative effect on me that—pain or no pain, impulse or no impulse—the idea of moving my leg did not come up again. I would venture the speculation that the building-up of the ideal ego in the very young child or infant comes about by a mechanism comparable to this response.

The second factor alleviating my insecurity was even more unexpected, had I been asked before the operation. Words spoken by medical friends present at the operation—even words I understood—had relatively little helping effect. But physical contact did have. One woman physician who assisted at the operation had to lean over me in such a way that she touched my arm. I remember her asking me at one time whether I minded that she had to lean over my arm and my reaction of astonishment at the question. I tried to figure out how to tell her what a great help it was to me. But in my over-anxiousness to make it clear to her, I could find no words at all. Much later she asked a second time and then I

asked her to stay as she was. (She was actually performing a difficult, prolonged task of retraction.)

Another woman doctor present at the operation touched my forehead once and said something, and I remember her touching me as a soothing event. Evidently friendly physical contact of this primitive type is not sufficiently recognized as a helpful procedure. I have since spoken to physicians who have undergone operations or performed them and they have confirmed my own experience in this respect.

My general mental condition during the operation and during the next 2 days and nights was much the same, with very little interest in the outside world. What preoccupied me most was what I would call pressures within the body. I had the typical postoperative difficulty in urination, a great difficulty of peristalsis, with gas formation, and some difficulty in breathing. All these pressures, as far as sensation goes, seemed to combine into one.

If I tried my best to answer a question about what my mood was during this period, I could not answer. One young doctor who gave me penicillin said, "In those days you were in the carrot stage." But the facial expression—mostly on account of pain—was apparently one easily confused with that of depression. As a matter of fact, one young physician said when he saw me again a few weeks later, "Well, now you're not gloomy any more." This shows a type of misjudgment important for the psychiatrist who does consultations in a general hospital and for the general practitioner. Actually, I was then in a stage far below that where there can be such clear-cut, differentiated emotions as depression with a content of intellectual worry.

At no time during this period were there any delirious or deliriod features. But one evening I thought I was confused. When the nurse who had looked after me following the operation came on duty the next day, there seemed to me something

strange about her. I was not sure whether she was the same person or not. She looked different, and I remember thinking that maybe I was mixing people up. I asked her. She laughed and said: "I just had a permanent wave." And so I was reassured.

While such comparisons should not be carried too far, the whole condition I have been describing invites one to view it in analogy with the mental state of a very young child who lives in a world of adults who talk of things he does not understand, hears words not always comprehended, reacts quickly to modulations of voices and physical comforting.

While I was still in a very serious physical state and a very reduced mental state, I had a dream. Later I interpreted it by free association.* When I woke up from this dream it seemed it had great significance for my life. Only a fragment of this dream and its interpretation are of interest here.

"I was talking to President Roosevelt. There was a question of what kind of speech he should make. I advised him to make about the same speech he had made a year ago, but to leave out the introduction. He took my advice, but added that he'd have to make an introduction which would take at least an hour. I advised him against this introduction. He offered me a cigarette. I told him I did not smoke."

Complete interpretation even of this fragment would be too long here. At first my free associations to Roosevelt seemed to lead me nowhere. Suddenly I realized that the President in this dream symbolized a man who had lost the use of his legs but carried on successfully despite it. In the dream, my being with the President was a grandiose idea; no less a person would do. In addition, further to exalt my ego, the situation is one in which he seeks my advice and I tell him what he should do. Obviously there was a compensatory mechanism at work at a time when my ego was crushed. This

mechanism meant a rallying of the ego. Such compensatory dreams in response to physical insult have been discussed by Federn.¹

The question of offering me a cigarette is a sign of cordiality; my saying that I do not smoke was tantamount to saying that I was a "good boy." Actually, I had stopped smoking over a year before. The question of smoking had been brought up by the doctors who examined me in the hospital, and therefore had considerable emotional interest for me. Other aspects of the interpretation of this "cigarette scene" in the dream are unimportant here.

There is also the angle that in the dream I tell myself: suppose I can't ever walk again; I can shift my abilities to the intellectual sphere to make up for what I will lose in the physical sphere.

From the many ramifications of this dream one more part has to be mentioned. I had this "recovery dream" while I was still very ill. But if this interpretation so far is correct, there would seem to be an interesting error. With me only one leg was affected; whereas with the President there were two. As a matter of fact, on the basis of slight sensations there, a vague fear of phlebitis in the other leg had been in my subconscious mind. In other words, this compensatory dream came at a moment when I feared the worst. The dream said: "even then, it won't be so bad."

Soon afterwards thrombophlebitis did become manifest in the left leg, and femoral ligation was carried out in that leg, too. Before the operation I received scopolamine, $\frac{1}{100}$ gr., and morphine, $\frac{1}{4}$ gr. The second operation also presented some complications and lasted longer than usual. My mental state during this operation was so abnormal that it deserves description.

I remember the very beginning of the operation and my general apprehension. But some time later I can still hear myself addressing the operating surgeon (whom I could not see): "I feel very frivolous,

* I discussed this dream and my free associations to it with Dr. Emil Gutheil.

Dr. D." This was a most abnormal statement to make. In the first place, I had and have the greatest respect for this surgeon and would not address him like that—certainly not during an operation. In the second place, I would say that "frivolous" was about the last word that would describe my mental state at that time.

From then on throughout the operation I laughed, told all sorts of funny stories and made puns. A considerable number of my medical friends were present in the operating room. They laughed at my jokes and told funny stories of their own. It all sounded very gay. On many occasions during this operation I suffered terrible pain. I tried not to show it, but could not help contorting my face and exclaiming "Ouch!" on a number of occasions. Anybody who did not see my face would think I was having a good time. One nurse, on the other side of the screen during the operation, told me later: "You were so cheerful and took it all so easily. I have never seen anything like it."

This state of mind has to be sharply differentiated from that of a manic or hypomanic. It is characteristic of a manic that he thinks things funny that are not funny at all.⁵ My jokes and puns were funny, and would have been appropriate had the situation been different. I also laughed heartily—and at the right moment—at the stories of others. There was no flight of ideas and no simple sound associations. An example of the pun I made: The pain after the first operation was relieved greatly by demerol. So I said during the second operation: "I have a new slogan. Don't get demoralized; get demerol-ized."

Toward the operation's end I suffered particularly severe pain during the ligation of the larger vessels. As I recall it, I was really in agony. At that worst moment, the internist who had been most appreciative of my actual pain, and helpful about it, saw my contorted face and said, "Anybody can tell stories like you

did. Now is the time to tell us a really good one, from your life as a psychiatrist."

If I were asked according to my best psychiatric judgment and according to my best knowledge of myself whether I would have been able to tell a funny story at that time or whether I could have even forced myself to smile at anything then, I would have denied it without hesitation. Yet fully preoccupied as I was with pain, I immediately told a story with great gusto and with all embellishments. This was the story. As a young doctor in Hopkins, I spent a vacation with a psychotic millionaire and his male nurse at a lodge in New Mexico. We had all our meals together in the general dining room. I noticed that when the waitress served us her hands trembled noticeably. After a few days of this, I asked her whether something was wrong. She said: "Well, it's like this. I know one of you is crazy, but I don't know which one it is."

There is evidence here of clear dissociation between actual mood and behavior. In general, my insight into my condition was very poor. I did not think of my behavior as being caused by a drug, although intellectually I might have guessed that. Yet I evidently had lucid moments with psychologic insight. For instance, at one moment I said to the surgeon, as if to excuse my "frivolity": "What I am really doing is whistling in the dark."

The term *euphoria* does not cover the whole of my behavior because at times I spoke seriously of serious things. In response to remarks made by physicians near me, I made true but most indiscreet comments on the treatment of mental patients in New York and where I believed the responsibility lay.

There were a number of things which I thought I'd only had in mind but which I was later told I had said aloud. There was also an incident where I *did* something which according to my memory I had only thought and talked about. When the operation was over I thought of getting up from the operating table, walking

across to the stretcher (which I thought was across the room) and getting up on it. This was a complete misunderstanding of the situation. I was in no condition to get up and the stretcher was right next to the operating table. I learned later that I actually attempted to sit up with this purpose in mind, and lay still only when told to do so. A few hours after the operation I returned to my normal state of mind and realized how abnormal my behavior had been.

The mental condition during the operation was a form of scopolamine psychosis. It was characterized by euphoria, overtalkativeness, general lack of inhibition, euphoric misjudgment of the situation, side by side with more or less clear consciousness of apprehension and pain and flashes of insight. There were no hallucinatory, delirious or dream-like experiences. This particular form of scopolamine psychosis with such a dissociation within the mental life I have not seen described before. It is probably only by self-observation that such a contradictory psychologic syndrome can be delineated; but it can be diagnosed objectively.

Actually, the euphorization of my behavior was a great help. What did it accomplish? It seems to me that it counteracted the anxiety which was undoubtedly present. While telling jokes or listening to them, I was distracted from anxiousness and the strain of experiencing pain. Such a contrast between euphoria and anxiety occurs in experimentally induced mescaline psychosis, as shown by the retrospective accounts of subjects.⁶

With regard to the subject of pain and analgesics, some of my observations are significant. I believe that in studies of pain, the threshold of pain is too much emphasized. Actually, the *quality* of pain is very important. I could, after this operation, have enumerated six or eight different kinds of pain, each sharply distinguishable from the other in quality. To express them in words would be impossible. Had I given each of these pains as they occurred a number, I believe an

observer would have found that I could have identified by its number the special type of procedure by its accompanying kind of pain.

Some of the qualities of pain are: (1) Localization (some I could not have localized at all; some I think I could have indicated exactly). (2) Duration. (3) "After-image" (I use this for want of a better term, because some kinds of pain continued even after I knew they were over. This is comparable to the phenomenon of after-images and eidetic images in visual perception. Such phenomena are easier to investigate in the sphere of vision, but exist also in other forms of sensation. It is possible that this type of pain refers to a more primitive, undifferentiated kind of sensation.^{7,8}) (4) Special qualities of pain, as when a nerve is touched. (5) Association with fear (some types of pain seem to be more associated with fear than others).

If psychologic factors play a great rôle in physical disease, as I believe they do, it may well be indicated to stimulate the productive activity of patients in the early stages of their physical disease. I believe that my interest in dictating these observations at the time (they were much more detailed than this paper would indicate, and the paper itself was written during my hospital stay) helped me to rally the recuperative forces of my organism. As Heine said:

"It was disease—the truth to tell—
Which gave impulse to my creation.
Creating, I got better.
Creating, I got well."

From a practical point of view, this study shows that there are definite and diversified psychiatric aspects of physical disease. Physicians are apt to neglect such experiences, but they are a grim reality. The psychopathologic aspects of physical disease demand and deserve attention. They may make the difference between life and death.

Medical and surgical patients need

psychologic advice about how they should act, what their experiences mean; they need psychologic preparation for what to expect; they need guidance so that they can make the best of the possibilities. As a physician, I was less handicapped in coping with these experiences than the general patient.

All these psychologic and psychopathologic features of physical disease are a part of medical and nursing care. It is a problem that can be attacked along three

levels: The first is the part of the nurse. The second is that of the medical man and the surgeon. The third is the part of the psychiatrist, who should be available for the diagnostically doubtful, the more severe and prolonged abnormal manifestations. Here is one phase of psychosomatic medicine which can be put into practice immediately without waiting for further investigation. Only in this way can psychiatry be really integrated in a general hospital.

REFERENCES

1. FEDERN, PAUL: A Dream Under General Anesthesia, *Psychiat. Quart.*, **18**, 422, 1944.
2. FREUD, S.: *Collected Papers*, IV. On Narcissism: An Introduction, 1914.
3. KRAEPELIN, E.: *Klin. Psychiat.*, vol. **2**, 1927.
4. WERTHAM, F. and F.: *The Brain as an Organ*, New York, Macmillan, 1934.
5. WERTHAM, F.: Prolonged Manic Excitements, *Am. J. Psychiat.*, **9**, 17, 1927.
6. WERTHAM, F., and BLEULER, M.: Experimental Study of the Influence of Mescaline on the Rorschach Test, *Arch. Neurol. and Psychiat.*, **28**, 52, 1932.
7. WERTHAM, F.: Eidetic Phenomena and Psychopathology, *Arch. Neurol. and Psychiat.*, **24**, 809, 1930.
8. WERTHAM, F.: Discussion, Psychosomatic Problems in Ophthalmology, *J. Clin. Psychopath.*, **6**, 477, 1945.

THIOURACIL EFFECT IN DIABETES MELLITUS COMPLICATED BY HYPERTHYROIDISM

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CONTROL of diabetes complicated by hyperthyroidism has always presented a difficult problem. Thyroidectomy has on occasion arrested the diabetes, rarely if ever cured it, and mostly rendered it less severe. Now comes thiouracil with its established positive action in controlling hyperthyroidism, offering the opportunity to observe its effect in ameliorating the profound action of hyperthyroidism and diabetes.

Six patients presenting this condition have been treated with thiouracil to control the thyrotoxicosis and the experience is described in the following detailed report:

Case Reports. CASE 1. T. J. D., a physician, aged 64, was first seen in September 1944 because of palpitation, sweating, exhaustion, tremor and a weight loss of 28 pounds during the past year. He had been under treatment for cardiac decompensation earlier in the year and was now on a daily maintenance dose of 3 gr. digitalis leaf. The diet, to which he claimed close adherence, consisted of P 70, C 150, F 150, with a single daily dose of 40 units protamine zinc insulin. Glycosuria was persistent in spite of these measures.

The diabetes antedated the hyperthyroidism which was first discovered about 20 years ago. Treatment with Lugol's solution was continued for 5 years and then stopped because of little benefit.

The patient was short, paunchy and gray-haired, with slight exophthalmos, lid-lag and conjunctival congestion. There was no palpable thyroid nor was substernal enlargement revealed by Roentgen ray. The palms were warm and moist with a fine tremor of both hands. The heart was normal in size, the sounds were distant, the rate was 100 with normal rhythm, and there were no murmurs. The prostate gland was smooth and both lateral lobes were enlarged.

The blood pressure was 120/100, the weight

187 pounds and the height 65 inches. The fasting blood sugar was 254 mg. %, there was a 4+ glycosuria and the BMR was +21%. Laboratory studies were otherwise within normal limits.

Digitalis was discontinued and thiouracil, 0.2 gm. 3 times daily, started. Three capsules of concentrated mixed vitamins were to be taken daily. Diet and insulin were continued as before. At the end of 2 weeks he reported less nervousness and agitation. In another 2 weeks the sweating had stopped and the tremor was gone; a fasting blood sugar was 166 mg. %, and the BMR was +26%. After 6 weeks of treatment all of his original symptoms had gone, he had gained 5 pounds in weight, the BMR was +14% and the urine had been sugar-free during the last 2 weeks. (He was examining 4 specimens daily.) The thiouracil was reduced to 0.2 gm. twice daily and insulin dosage cut to 30 units PZI daily. In another 2 weeks the BMR was +10%, the weight had increased another 3 pounds and the glycosuria continued. A fasting blood sugar was 104 mg. %. He was entirely symptom-free. Insulin was reduced to 10 units PZI daily and the thiouracil to 0.1 gm. 3 times daily, but at the end of 2 weeks the BMR was +23% so the thiouracil was increased to 0.1 gm. 4 times daily which has since been continued as a daily maintenance dose. The insulin was discontinued at this time (after 10 weeks treatment) and the diabetes has remained controlled by diet alone. Several fasting blood sugar determinations made at monthly intervals were 114, 136, 125, 121 and 118 mg. %. The BMR has ranged between -2 and +12% and reached +23% once when the dose of thiouracil was reduced to 0.3 gm. daily. The thyroid gland, which could not be palpated, developed bilateral palpable enlargement during the 8th month of treatment.

After 9 months treatment this patient is symptom-free. He has gained 13 pounds, his BMR is +10%, and to all appearances

the thyrotoxicosis is in remission and the diabetes under satisfactory control.

CASE 2. R. B. K., white male, aged 45, has been under observation since December 1935, when he first developed weakness, polyuria, polydipsia and weight loss of 15 pounds. In November 1933, he had developed the full-blown picture of exophthalmic goiter and thyroidectomy was performed in January 1934. This was followed by improvement until July 1935, when the goiter returned along with many of the previous symptoms. Lugol's solution controlled this disturbance for the next 4 months and then, following an attack of sore throat and "intestinal flu," it lost its effectiveness and he started a downhill course which terminated with symptoms of diabetes.

The patient was short, stocky and overly alert. The breath had an acetone odor. There were marked exophthalmos and lid-lag, bilateral smooth thyroid enlargement, tachycardia and warm moist palms with fine tremor. The tonsils were badly infected and the teeth decayed, with marked gingivitis. The blood pressure was 150/90, the BMR +32%, and a fasting blood sugar 190 mg. %. He weighed 135½ pounds.

He was hospitalized for 1 week during which he responded well to bed rest, diet and insulin. When discharged he was on a diet of P 73, C 118, F 135, with 25 units regular insulin 3 times daily. This was gradually reduced to 10 units 3 times daily during the next 2 weeks. Lugol's solution was now resumed and the improvement further accelerated. Within 1 month the weight had increased 5 pounds, the BMR was +24%, the urine showed only occasional traces of sugar and the goiter symptoms had largely subsided. At the end of another month the condition had improved markedly and tonsillectomy was performed without mishap. He continued to gain steadily, the diabetes soon was controlled without insulin even with a gradual increase in the carbohydrate and fat of the diet. The hyperthyroidism continued in remission while taking 3 drops Lugol's solution daily. This satisfactory state continued 3 months, when glycosuria reappeared requiring 17 to 20 units regular insulin daily for control. In December 1936, the regular insulin was replaced by 10 units of protamine insulin but control was unsatisfactory. During January 1937 a dose of 7 units regular insulin

was given in the morning and 8 units crystalline insulin (Stearns) in the evening, again with unsatisfactory results. Successively protamine insulin, 2 doses daily, was tried, followed by 1 dose of protamine in the evening and 1 of regular insulin in the morning; then the 2 were given at the same time in the morning and this appeared to effect better control although the dosage had to be increased to 10 units regular and 20 units protamine. This latter was replaced by protamine zinc insulin in January 1938.

Control of the diabetes was nevertheless far from satisfactory and although the thyrotoxicosis appeared controlled a loss of effectiveness of the Lugol's solution was feared as was the development of a state of iodine fastness or resistance. Since the patient objected to thyroidectomy, a course of 6 Roentgen ray treatments was administered during a period of 3 months in late 1938 and early 1939. There was no evident change following this therapy. The thyroid which had previously diminished in size and increased in hardness with the continuous iodine therapy now became somewhat smaller. Exophthalmos, tachycardia and tremor reappeared gradually, the BMR reached a level of +50% and the diabetes required increasing doses of insulin for control (35 units regular and 35 units PZI daily).

Thyroidectomy was performed in November 1939 and the patient made an uneventful recovery. The diabetes, however, did not improve, in spite of the abatement in thyrotoxicosis. Control became increasingly "hair trigger" and was now more and more difficult, requiring varying and increasing amounts of both regular and protamine zinc insulin. To add to these difficulties, exophthalmos of the right eye began to develop 6 months after thyroidectomy and, although it appeared advisable to administer thyroid extract for its control, this was not done for fear of further disturbing the diabetes.

The unilateral exophthalmos increased during the next 6 months, the blood cholesterol reached a level of 344 mg. % and the BMR -15%; the weight increased 6 pounds and there was now sensitivity to cold with sluggishness, and puffiness of the upper eyelids. Frequent hypoglycemic reactions alternated with high blood sugar levels and almost constant glycosuria. ½ gr. thyroid extract daily was started and striking improvement of all symptoms followed after

1 month. With increase to $\frac{1}{2}$ gr. thyroid extract twice daily the improvement was maintained without appreciable change for the next 3 years and 10 months, although the diabetes now required 50 units PZI and 6 units crystalline insulin daily for fair control that was interspersed with frequent hypoglycemic reactions. (Globin insulin was tried for a time without success.)

In December 1944 there was noticeable nervousness and exophthalmos with tremor, tachycardia and warm moist palms. The BMR was +9%. (Thyroid extract had been discontinued 1 month before because of a suggestion of nervousness, tremor and mild tachycardia.) Thiouracil, 0.1 gm., 3 times daily, was started and within 4 weeks the symptoms had abated and the BMR was -16%. The dosage of thiouracil was reduced to 0.1 gm. twice daily and continued at this level for the next 6 months, the BMR varying between +7 and -1%. With an increase to +11% early in June 1945, thiouracil was increased to 0.1 gm. 3 times daily which is the present maintenance dose.

In the 6 months of thiouracil therapy the weight had increased 16 pounds and all evidence of thyrotoxicosis, including exophthalmos, had disappeared. The diabetes was somewhat less severe in that a fair measure of control could be maintained with 38 units PZI and 10 units crystalline insulin daily.

In this patient with primary hyperthyroidism that antedated his diabetes, improvement in the latter condition followed initial dietetic restriction, insulin and Lugol's solution. Gradually, however, even under continued iodine administration, then Roentgen ray therapy, thyroidectomy and finally thiouracil, the diabetes slowly increased in severity and now, despite the remission in the thyrotoxicosis, it still presents a difficult management problem.

CASE 3. C. C., white male, aged 41, first came under observation in January 1936, when he had an acute upper respiratory infection with right-sided pleurisy and effusion. He had had diabetes mellitus for 8 years, was not adhering closely to his diet and was maintaining varying control by using 50 units regular insulin divided into 2 doses. There was fever and acidosis and the blood sugar level was 388 mg. %. Large doses of insulin and ample fluids cleared the acidosis and gradually brought the diabetes

under control. However, following release from the hospital he continued to show marked fluctuation in blood sugar level and was having frequent reactions in spite of redistribution of the diet (P 70, C 150, F 130) and variation in dosage and timing of insulin. He was shifted from regular to crystalline, to protamine and to protamine zinc insulin at the time when these first became available. A fairly good degree of stabilization was finally achieved in September 1937 by the administration of 30 units crystalline insulin in the morning and 20 units 12 hours later. He gained some weight on this régime but began to manifest nervousness and a slight tremor of the hands in November 1937. The skin was warm and the palms moist, but there were no eye signs, the thyroid was not palpable and there was no tachycardia. The blood pressure, however, changed from a range of 110 to 140 systolic and 60 to 90 diastolic to 150 to 170 systolic and 80 to 90 diastolic. The BMR was +22%.

A course of physostigmine salicylate, $\frac{1}{32}$ gr. 3 times daily, was followed for 15 months without effect on the hyperthyroidism. Shortly after discontinuing this treatment and following a change in jobs to one requiring greater physical exertion hypoglycemic reactions increased and crystalline insulin was reduced to 20 units every 12 hours. There were fewer reactions and the control of the diabetes was fair for the next year although there was a gradual loss of 14 pounds in weight, with tachycardia, tremor, sweating and a high pulse pressure. There was still no palpable thyroid or characteristic eye signs. Two BMR determinations made 1 week apart were +35 and +41% (1940). Three drops Lugol's solution were given daily and at the end of 2 months the BMR was +16%, the tachycardia was diminished, sweating and tremor had stopped and there were fewer hypoglycemic reactions. At this time (1940) Althausen¹ announced the galactose tolerance test for differentiating glycosuria of diabetes mellitus from that due to hyperthyroidism. The test was performed on this patient with a reading of 34.72 at $\frac{1}{2}$ hour and 38.44 mg. % at the end of 1 hour—indicating the presence of hyperthyroidism.

The patient continued taking 3 drops Lugol's solution daily and 20 units of crystalline insulin every 12 hours for the next 41 months. He regained his lost weight,

and his diabetes was quite well controlled. At this time the thyroid gland became palpable and both lobes felt nodular.

Thiouracil replaced the Lugol's solution in August 1943 and was given in a dose of 0.2 gm. 3 times daily. The BMR at this point was +13% and the blood cholesterol level 250 mg. %. A slow rise in the BMR followed, readings taken every 2 weeks being +14, 10, 18 and 26%, with no change in the general condition. This unusual reaction to thiouracil may have been due to the prolonged iodization but subsequent failure to effect a lowering of the BMR throughout a 20 month period of observation, even with doses of thiouracil up to 1.2 gm. daily, and substitution of thiourea for thiouracil, is not easy to explain. The patient either must have an inherent resistance to these drugs, or one acquired through the prolonged administration of iodine; or the elevated BMR may indicate disturbed metabolism other than that due to hyperthyroidism. With the latter condition in remission, failure to respond in expected fashion becomes understandable.

Since discontinuing treatment for the thyrotoxicosis and with only diet and insulin, there has been maintenance of weight and no evidence of hyperthyroidism, while the diabetes has remained well controlled.

In this patient with the diabetes present before the secondary hyperthyroidism, remission of the latter condition through the use of iodine has made possible smooth, effective control of the diabetes. An attempt to substitute thiouracil and thiourea for the iodine met with failure due to resistance, possibly natural, but more probably due to the prolonged iodization and the presence of a state of remission (in spite of an elevated BMR).

CASE 4. C. M., a white female, aged 50, first came under observation in May 1944 because of increasing pallor, weakness and anorexia during the previous 6 months, and an attack of nausea and vomiting during the previous 24 hours. She had had a thyroidectomy for exophthalmic goiter in 1928, a tonsillectomy the same year, a hysterectomy in 1934, an attack of arthritis in 1938, and diabetes of short duration successfully controlled by diet alone, in 1942.

The skin had the characteristic waxy yellow color of primary anemia. There was no palpable thyroid tissue and no exophthal-

mos or tremor. There was a rough systolic murmur at the apex, normal rhythm and an increase in rate. The reflexes were normal. Laboratory studies revealed achlorhydria; hemoglobin 45% (Sahli), with r.b.c. 1.55 million (color index of 1.5) and marked anisocytosis. With absence of parasites and occult blood in the stool and negative findings on Roentgen ray study of the gastrointestinal tract, a diagnosis of primary (Addisonian) anemia was warranted and was further confirmed by the characteristic reticulocyte response that followed the parenteral use of liver extract. She remained in the hospital 12 days and improved markedly while there.

A fasting blood sugar was 192 mg. % with the urine negative for sugar 2 days after admission. A BMR was +27% and a blood cholesterol 277 mg. % on the same day. The day of discharge the BMR was -5%. The weight was 172 pounds.

Improvement continued with weekly injections of 15 units concentrated liver extract and at the end of 8 weeks the red cell count had reached a level of 5.46 million and the hemoglobin 86% (Sahli). Progress was uneventful until December 16, 1944, when she complained of insomnia, shakiness and trembling. There was a weight loss of 2 pounds in the past month, the blood pressure was 146/80, and the pulse rate 100. A fine tremor of the hands was present. With mild sedation during the following month, she reported improvement but had lost another 2 pounds. The pulse was still rapid and the tremor of the hands marked. In February 1945, although she still reported improvement, she had again lost 2½ pounds, the tremor was still present, the pulse rate was 136 and the BMR +22%. There were no eye signs and no palpable thyroid tissue.

One-tenth gm. thiouracil was administered twice daily during the next month. By March 23, 1945, she had lost another 2 pounds, but the BMR was now +17%, the pulse rate 100, blood pressure 110/70, and there was no tremor or nervousness. Thiouracil was increased to 0.1 gm. 3 times daily. One week later she began to notice increasing urinary frequency, then polyuria, polydipsia and finally vaginal pruritus. When seen on April 20, she had lost 7 pounds, the fasting blood sugar was 258 mg. %, there was marked glycosuria, but no tremor or nervousness and no tachycardia. The hemo-

globin was 104% (photoelectric) and r.b.c. 7.01 million. The blood pressure was 120/80 and the BMR was now +3%.

This turn of events, a flareup having every appearance of a true diabetes mellitus following closely upon the thiouracil induced remission in the hyperthyroidism, strongly suggested stimulation of the anterior pituitary not only to produce more thyrotropic hormone but to augment its contra-insular action. This sudden precipitation of diabetes seemed analogous to that which develops in Houssay animals by the injection of anterior lobe extracts, with protein constituting the sole source of the excreted glucose.⁷

The use of insulin was deferred and a diet consisting of P 80, C 100, F 40 prescribed, with the thiouracil continued as above. Two weeks later, May 4, 1945, there was a 3 pound weight loss, a fasting blood sugar level of 193 mg. %, decreased glycosuria, and a marked diminution in the polyuria, polydipsia and pruritus. The BMR was now +20% but there was no nervousness, tachycardia or tremor. In 2 more weeks (May 18) the weight had fallen another 4 pounds but the fasting blood sugar was 160 mg. % with no glycosuria and no diabetic or hyperthyroid symptoms. The BMR was now +5%. During the next 6 weeks the weight dropped 5½ pounds, she was aglycosuric with a fasting blood sugar level of 169 mg. % and was feeling fine with no subjective or objective disturbance. The BMR was +24%. The diet was increased by 45 gm. carbohydrate but the rest of the treatment remained the same. At the end of 10 days she had regained 5 pounds and continued symptom-free. The BMR was now +15%. Apparently the disturbance, appearing first as a recurrent hyperthyroidism, then as a precipitate diabetes, was subsiding and gradual increase in the diet to supply the caloric need was being instituted while continuing with thiouracil to suppress the hyperthyroidism.

This patient with primary hyperthyroidism treated by thyroidectomy 17 years ago, developed diabetes 2 years ago which was successfully controlled by diet alone and apparently subsided. Fourteen months ago she was found to have a primary anemia that responded to specific therapy and has remained under control with continuous parenteral liver therapy. Five months ago she showed evidence of recurrent hyperthyroid-

ism which subsided appreciably after 4 weeks of thiouracil. A week later full blown diabetes developed suddenly which is now controlled by diet alone while thiouracil is still being administered. The primary anemia continues under control by means of liver extract.

Appearance of the diabetes 5 weeks after continuous thiouracil may well have resulted from stimulation of the anterior pituitary through thiouracil suppression of the thyroid. Thus the thiouracil cannot be credited with an immediate assist and its rôle at best lies in rendering indirect aid through suppression of the hyperthyroidism.

(An interesting speculation regarding the combination of primary hyperthyroidism, diabetes and primary anemia may be offered with the liver in the rôle of chief target organ. The hyperthyroidism with the associated hyperfunction of the anterior pituitary may well have produced liver damage⁸ with ultimate impairment in carbohydrate metabolism and impaired storage capacity for the intrinsic anti-anemic factor.)

CASE 5. M. G., a white female, aged 57, was referred by her physician, May 29, 1945, because of difficulty in controlling diabetes mellitus which had been discovered some 6 weeks earlier. There was weakness, exhaustion, some weight loss, increased appetite, polyuria, polydipsia and vaginal pruritus. The history disclosed chorea at the age of 12; a small goiter for as long as she could remember (one BMR 8 years ago was reported normal); and treatment for hypertension during the past year.

The patient was quite nervous and her voice was tremulous. She weighed 147½ pounds, was 63½ inches tall, showed a slight stare with lid-lag, moist warm palms with a fine tremor, and bilateral irregular-nodular enlargement of the thyroid, partly substernal. The blood pressure ranged from 180 to 170 systolic and 120 to 110 diastolic. The eye-grounds showed very little arterial change. The fasting blood sugar was 178 mg. %, with aglycosuria. The BMR was +15%.

A diet of P 70, C 100, F 40 was prescribed and the patient started on 0.2 gm. thiouracil 3 times daily, a capsule of mixed vitamin concentrates to be taken with each dose. At the end of 2 weeks she reported decrease in nervousness, palpitation and the urinary disturbance. The blood pressure was 160/80,

the pulse rate 90, the BMR +7% and the fasting blood sugar 132 mg. %. The urine had shown only an occasional trace of sugar. The weight was down to 144 pounds and the thyroid was softer and slightly larger. At the end of another 2 weeks the weight was 139½ pounds, the pulse 76, blood pressure 140/90, BMR +7% and fasting blood sugar 139 mg. %. There was still occasional glycosuria. She was sleeping better, was less nervous, the voice was stronger and her strength was returning. No tremor or palpitation was noted. The thyroid was somewhat larger and softer.

Thiouracil was reduced to 0.2 gm. twice daily and at the last examination, July 10, 1945, the weight was 140 pounds, blood pressure 140/90, pulse 64, fasting blood sugar 128 mg. % with constant aglycosuria and the BMR -8%. There were no disturbing symptoms and to all appearances the diabetes had come under control while the hyperthyroidism was in remission.

This patient with diabetes mellitus aggravated by a secondary hyperthyroidism responded promptly to dietetic management as the hyperthyroidism was brought under control with thiouracil.

CASE 6. M. M., a white female, aged 26, first complained of weakness and exhaustion in the fall of 1941. Gradually she developed polyuria and polydipsia, and lost about 10 pounds in weight by January 1942. At this time she had marked glycosuria with a fasting blood sugar level of 200 mg. %. The BMR was zero. The weight was 90 pounds.

A diet of P 60, C 125, F 100 was prescribed and she was to take 10 units PZI daily. Improvement was marked in a very short time. There was weight gain, with aglycosuria and cessation of disturbing symptoms. The diet was gradually increased to P 70, C 150, F 130 and she remained aglycosuric while taking between 5 and 7 units PZI daily. Gradually, however, control became increasingly difficult and she failed to gain weight in spite of an increase in diet to P 100, C 150, F 170, with a dose of 10 to 12 units PZI and 5 to 10 units crystalline insulin. There were occasional hypoglycemic reactions and these continued to recur during the next 20 months while she was out of the city.

On her return May 29, 1945, she weighed 95½ pounds, was still having difficulty controlling the diabetes in spite of a present

dose of 12 units PZI and 22 units crystalline insulin (1 injection). A fasting blood sugar was 204 mg. %.

She was hospitalized for 10 days and although she was ambulatory it was still difficult to achieve control of the diabetes. During this time it was noted that her palms were warm and moist and showed a fine tremor. The eyes too were somewhat brighter than formerly, although there was no exophthalmos or lid-lag. Neither was there any palpable thyroid tissue. A BMR was +10% June 8, +12% June 10 and 11.

In the belief that a mild hyperthyroidism was interfering with diabetic control, the patient was started June 12 on 0.2 gm. thiouracil 3 times daily. The weight was 96 pounds and the insulin dosage was now 13 PZI and 26 crystalline units (1 injection). At the end of 1 week the weight was 98½ pounds, the fasting blood sugar 151 mg. % and she was spilling less sugar. The BMR was +11%. The palms were still warm and moist but there was no tremor. After another week the weight was 98 pounds, the fasting blood sugar 105 mg. %, there was very little glycosuria, and no tremor while the palms were now cool and dry. The BMR was +12%. The thiouracil was now reduced to 0.2 gm. twice daily. Two weeks later the weight was 100 pounds, the fasting blood sugar 63 mg. %, with complete aglycosuria. The BMR was +5%. She was feeling well and showed no evidence of hyperthyroidism. Evidently, since this was the first time in several years she had remained continuously aglycosuric for 2 weeks, it was believed that the suppression of the very mild hyperthyroidism by thiouracil had aided in the control of the diabetes.

In this patient the diabetes was difficult to control until a remission of the mild secondary hyperthyroidism was induced through the use of thiouracil.

Summary and Conclusions. Of the 6 patients, 3 (Nos. 1, 5 and 6) showed improved control of the diabetes following the remission in the hyperthyroidism induced by thiouracil. A fourth (No. 3) also showed improvement but the remission in the thyrotoxicosis had been previously induced by iodine and not by thiouracil. The remaining 2 patients (Nos. 2 and 4) failed to respond favorably to the treat-

ment, which in Patient 4 may even have served indirectly to reactivate a latent diabetes.

It is especially significant that the 4 patients who improved all had secondary hyperthyroidism (toxic adenoma) which became manifest after the diabetes had appeared. The 2 patients classed as failures had primary hyperthyroidism (exophthalmic or toxic diffuse goiter) which antedated the diabetes in each instance. Evidently this latter type of patient, in which the disturbance is polyglandular, fails to respond satisfactorily to any known form of treatment—as in the case of Patient 2 who had had two thyroidectomies, iodine, roentgen ray therapy and thiouracil.

A review of the reported thiouracil treated cases of diabetes and hyperthyroidism discloses both successes and failures. When these are classified as to type of hyperthyroidism, the validity of the above mentioned observation becomes apparent. Astwood's² patient with secondary hyperthyroidism, in whom the diabetes preceded the thyrotoxicosis by 10 months, was able to discontinue the use of protamine zinc insulin altogether. The patient reported by Kahn and Stock⁵ had a toxic diffuse goiter antedating the diabetes which was difficult to control. Rose and McConnell's⁹ patient in whom treatment failed to improve the diabetes was a 13 year old girl with primary hyperthyroidism. (This had become evident

11 months after the onset of diabetes.) They make the interesting comment that "possibly the production of increased diabetogenic activity in the pituitary by thiouracil may have prevented amelioration of the diabetes." McGavack⁸ reports no expected improvement in any of 4 diabetics, and in 1 the tolerance decreased without known cause. Only 1 of the 4 patients is reported as having had toxic diffuse goiter. The type of goiter in the other 3 patients is not described.

Eaton³ treated 4 patients who had diabetes and found that the 3 patients who responded well had secondary hyperthyroidism while the 1 that did not respond had primary hyperthyroidism. Fishberg and Vorzimer⁴ report 2 diabetic patients with secondary hyperthyroidism in whom the diabetes came under better control after thiouracil therapy.

Of the 13 patients reported in the literature, 4 responded favorably while 9 failed to show improved control of the diabetes. With the 6 patients reported here the total is 19, of which 8 were improved (1 of these with iodine), and 11 not improved.

Evaluation of the effectiveness of thiouracil in this small series of cases would place it on a comparable level with thyroidectomy where the hyperthyroidism is secondary. In primary hyperthyroidism, or exophthalmic goiter, while it does control the toxicity, it exerts little favorable influence on the control of the associated diabetes.

The thiouracil was supplied by the Lederle Laboratories, Pearl River, N. Y.

REFERENCES

1. ALTHAUSEN, T. L., LOCKHART, J. C., and SOLEY, M. H.: New Diagnostic Test (Galactose) for Thyroid Disease, *AM. J. MED. SCI.*, 199, 342, 1940.
2. ASTWOOD, E. B.: The Treatment of Hyperthyroidism With Thiourea and Thiouracil, *J. Am. Med. Assn.*, 122, 78, 1943.
3. EATON, J. C.: Treatment of Thyrotoxicosis With Thiouracil, *Lancet*, p. 171, Feb. 10, 1945.
4. FISHBERG, E. H., and VORZIMER, J.: Extrathyroid Effects of Thiouracil Therapy, *J. Am. Med. Assn.*, 127, 915, 1945.
5. KAHN, J., and STOCK, R. P.: Fatal Agranulocytosis Resulting From Thiouracil, *J. Am. Med. Assn.*, 126, 358, 1944.
6. KORENCHESKY, V., and HALL, K.: Histological Changes in the Liver and Kidneys of the Rat After Administration of Thyroid Hormone and Vitamins, *Jour. Path. and Bact.*, 56, 543, 1944.
7. LONG, C. N. H.: Recent Advances in Carbohydrate Metabolism With Particular Reference to Diabetes Mellitus, *Ann. Int. Med.*, 9, 166, 1935.
8. MCGAVACK, T. H., GERL, A. J., VOGEL, M., and SCHWIMMER, D.: The Treatment of 26 Thyrotoxic Patients With Thiouracil and a Review of Toxic Reactions in All (35) Reported Cases, *Jour. Clin. Endocrinol.*, 4, 249, 1944.
9. ROSE, E., and MCCONNELL, J.: Thiouracil in the Treatment of Thyrotoxicosis. Clinical Experience with 37 Cases, *AM. J. MED. SCI.*, 208, 561, 1944.

THE INFLUENCE OF ENVIRONMENTAL TEMPERATURE AND RELATIVE HUMIDITY ON THE RATE OF WATER LOSS THROUGH THE SKIN IN CONGESTIVE HEART FAILURE IN A SUBTROPICAL CLIMATE*†

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THE problem of water balance in congestive heart failure is relatively little understood. This is essentially true also for thermal regulation. That thermal regulation is disturbed in congestive heart failure has been established by clinical observations and in particular by the studies of Steele and Cohn,^{3,9,10} although Kinsey and White⁷ regard fever of more than 1° F. as being due to a complication of failure. The former group of observers noted the development of fever in uncomplicated congestive heart failure, even in the cool climate of New York City. They concluded that the elevation in body temperature resulted mainly from disturbances in the circulation concerned with the elimination of heat *via* the skin. That the rate of heat production may be increased in congestive heart failure is generally accepted. In considerations of water balance and thermal regulation the factors of sweating and the evaporation of water from the surface of the skin have been neglected. Furthermore, the influence of environmental temperature and relative humidity and subtropical and tropical climates on congestive heart failure in general, and thermal regulation and water loss from the skin in particular, have received little serious attention. It is the purpose of this report to present the results of observations conducted to understand more clearly the above mentioned phenomena.

Methods and Materials. The method employed to measure the rate of water loss was that previously described.⁵ The method consists essentially of directing dry oxygen

by means of suitable tubing and metal chambers² over known areas of skin to collect surface water. The water-laden oxygen is then conducted through aluminum coils cooled in carbon dioxide snow where the water condenses. The water collected in the coils is measured gravimetrically.

The areas studied were the tip of the right index finger, the pretibial area of the middle portion of the right leg and the volar surface of the right forearm.

The subjects rested for 1 hour in a hospital type of bed in an air-conditioned room free from perceptible movements of air. During the period of rest, the metal chambers isolating the areas of skin for study were sealed in place. The room air was comfortable during this time and during the first measurements, the conditions being: mean temperature 21.3° C., range 20 to 22.8; mean relative humidity 60.2%, range 48 to 72. The rate of water loss was then measured for the three areas (finger tip, leg, and forearm) simultaneously, three successive 15-minute collections being made. The room conditions were then made hot and humid within a period of 15 to 20 minutes. The room conditions were changed to: mean temperature 40.2° C., range 37.2 to 42.2; mean relative humidity 64.2%, range 52 to 72%. When these conditions were attained three successive simultaneous 15-minute measurements of the rate of water loss were then made for the three skin areas.

The subjects studied consisted of 11 normal adults varying in age from 22 to 41 years, 9 were males and 10 were white. There were 10 subjects suffering from various diseases (diabetes mellitus, subacute glomerular nephritis, psychoneurosis, chronic hepatitis, fever, pernicious anemia, senility and acute rheumatic fever) but free from congestive heart failure. These subjects varied

* Aided by a grant in aid by the Helis Institute for Medical Research and the Rockefeller Foundation.

† This is the 16th paper published from this Laboratory of Tropical Physiology.

from 17 to 64 years of age, 4 were males and 2 were white.

There were 20 patients who suffered from right and left ventricular congestive heart failure. These were divided according to the degree of failure at the time of study. Five patients (12 to 58 years of age, 2 males and all negro) had mild to no failure, *i. e.*, Functional Class I and II of the American Heart Association criteria for the classification of heart failure. Five patients (28 to 52 years of age, 2 males and 4 negroes) had a moderate amount of failure, *i. e.*, Functional Class III. Ten patients (30 to 65 years of age, 5 males and 9 negroes) suffered with severe failure, *i. e.*, Functional Class IV.

All of the patients with congestive heart failure had entered the hospital in Class IV failure, but some of them had recovered to Class I, II or III failure. The edema and general condition of some of the 10 patients in Class IV failure was improving, while in others the edema and general state of the heart failure was becoming progressively worse. Since it was necessary to move these patients from the wards of Charity Hospital to our laboratory at the Tulane Medical School, none of the patients were in a moribund state, that is suffering from extreme air hunger and circulatory collapse. They were not experiencing cold sweating. Three of the patients were receiving oxygen. This was discontinued during the studies without unfavorable results. All of the 20 subjects were on a therapeutic régime for congestive heart failure. This included the use of digitalis and diuretics; the latter drugs were used in only some instances.

All rates of water loss were expressed in milligrams per 10 sq. cm. of surface area per 10 minutes. The surface area of the finger tip was calculated by the method previously described.^{1,6}

Results. These are summarized in Tables 1, 2 and 3, and Figures 1, 2, 3 and 4.

The mean rate of water loss from the skin of the right index finger tip, volar surface of the right forearm and anterior surface of the right leg was 10.7, 5.4 and 5.3 mg. per 10 sq. cm. of skin surface per 10 minutes respectively for the normal subjects in a comfortable environment (Table 1 and Fig. 1). The ranges were 7 to 17.7, 3.5 to 8.7 and 3.1 to 8.3 respec-

tively. In a hot and humid environment, the normal subjects lost water from the three areas of skin at a mean rate of 28.3, 31.5 and 39.9 mg. per 10 sq. cm. per 10 minutes respectively for the finger tip, forearm and leg. This represents an increase of from about 3- to 8-fold (Table 1). In the comfortable environment, there was no visible sweating, while in the hot and humid environment, sweating was not only visible but profuse. These differences in the rates of water loss are graphically illustrated by Figure 1.

The patients with severe congestive heart failure resting in a comfortable environment lost water at a mean rate of 5.4, 4.9 and 4.4 mg. per 10 sq. cm. of skin surface per 10 minutes for the finger, forearm and leg respectively. The ranges for the 3 parts were 3.8 to 8.1, 1.6 to 7.2 and 1.9 to 6.3, respectively. In a hot and humid environment, the mean rates of water loss for the skin of the 3 parts were 13.2, 10.8 and 10.8, the range being 10.6 to 17.4, 7.5 to 15.5 and 6.7 to 19.1 respectively (Table 3, Fig. 1). These patients showed no signs of visible sweating in the comfortable environment and very little visible sweating in the hot and humid environment. The percent increase in the mean rates of water loss in the hot and humid environment for the finger tip, forearm and leg were only 46.6, 34.3 and 27.1 respectively of the rate for these three areas in the normal subjects. The relative rates of water loss in the normal subjects and patients with congestive heart failure are shown by Figure 1. The rate of water loss in comfortable environment tended to be less in the patients with congestive heart failure than in the normals.

Table 3 and Figures 3 and 4 show the rates of water loss in mild, moderate and severe congestive heart failure. As the degree of heart failure decreased, the rate of water loss in the hot and humid environment approached normal. In the patients with moderate failure, the mean rates of water loss from the finger tip, forearm and leg for the hot and humid

atmosphere were 62.5, 75.6 and 60.7% respectively of the normal rates under similar conditions. In the patients with mild failure, the mean rates were normal.

In the patients with miscellaneous diseased states other than congestive heart failure the rates of water loss in the comfortable and hot and humid atmospheres were found to be within normal variations (Table 2 and Fig. 2).

It is well to note that in all of the groups of subjects studied, there were individual instances of overlapping of rates. However, in the patients with severe congestive failure there was a consistent impairment of water loss in the hot and humid environment.

General Reaction to Hot and Humid Environment. During the course of these studies, the subjects were observed as to

TABLE 1.—THE RATES OF WATER LOSS (MG. PER 10 SQ. CM. OF SURFACE AREA PER 10 MIN.) MEASURED SIMULTANEOUSLY FROM THE SKIN OF 3 WIDELY SEPARATED AREAS OF 11 NORMAL SUBJECTS

Subject				Parts studied								
				Finger			Forearm			Leg		
				C	H. & H.	H.H.:C	C	H. & H.	H.H.:C	C	H. & H.	H.H.:C
1	26	M	W	8.6	17.8	2.1	5.6	8.3	1.5	5.6	10.4	1.9
2	35	F	W	10.4	46.7	4.5	8.7	75.6	8.7	8.3	76.8	9.3
3	22	M	W	7.0	33.6	4.8	4.0	37.7	9.4	3.1	40.1	12.9
4	24	M	W	17.7	42.3	2.4	3.5	32.5	9.3	4.0	30.4	7.6
5	22	M	W	11.7	17.5	1.5	5.7	44.4	7.8	3.6	46.0	12.8
6	22	M	W	7.9	25.3	3.2	5.7	37.3	6.5	6.9	42.8	6.2
7	41	F	C	7.3	17.4	2.4	5.7	26.4	4.6	6.1	38.0	6.2
8	24	M	W	7.7	32.7	4.2	5.2	17.5	3.4	5.3	17.5	3.3
9	23	M	W	12.4	30.2	2.4	4.4	35.3	8.0	5.1	45.1	8.8
10	23	M	W	17.2	29.5	1.7	3.5	9.2	2.6	3.5	34.8	9.9
11	22	M	W	9.2	18.4	2.0	6.9	22.3	3.2	6.6	57.3	8.7
Mean	10.7	28.3	2.8	5.4	31.5	5.9	5.3	39.9	8.0
Max.	17.7	46.7	4.8	8.7	75.6	9.4	8.3	76.8	12.9
Min.	7.0	17.4	1.5	3.5	8.3	1.5	3.1	10.4	1.9

C = Comfortable environmental conditions. H. & H. = Hot and humid environmental conditions. H.H.:C = Ratio of rates in hot and humid environment to that in comfortable environment.

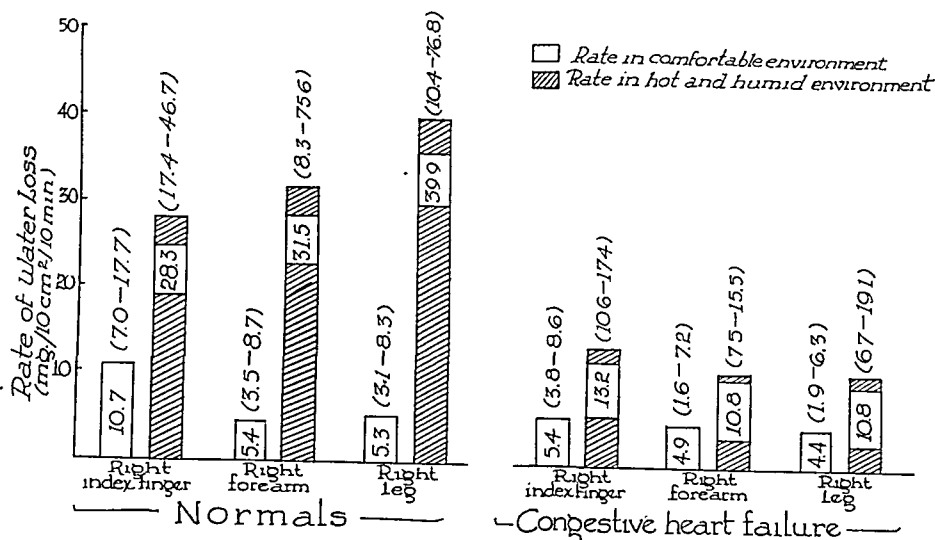


FIG. 1.—The rates of water loss in normal subjects and patients with left and right ventricular congestive heart failure (functional Class IV). The mean values are indicated in the bars and the extremes are enclosed in the parenthesis.*

* This applies for all figures.

their reaction to the two conditions of the room. With few exceptions, the subjects preferred the comfortable room conditions. There were 3 negro patients who preferred the hot and humid room conditions during the period of study and rest, although they admitted it would not be satisfactory were they at work or

moving around. These 3 subjects found the temperature of 20° C. (68° F.) uncomfortably cool. All subjects with the exception of those in severe congestive heart failure, withstood the hot and humid environment fairly well, although most of them found it very uncomfortable. They complained of restlessness,

TABLE 2.—THE RATES OF WATER LOSS IN 10 PATIENTS WITH VARIOUS DISEASED STATES OTHER THAN CONGESTIVE HEART FAILURE

Subject				Parts studied									Diagnosis
				Finger			Forearm			Leg			
No.	Age	Sex	Color	C	H. & H.	H.H.:C	C	H. & H.	H.H.:C	C	H. & H.	H.H.:C	
12	53	F	C	9.4	49.5	5.3	5.1	31.6	6.2	5.3	31.9	6.0	Diab. mellitus
13	14	F	C	2.9	48.5	16.7	4.0	33.3	8.3	1.3	32.9	25.3	Subacute glom. neph.
14	45	M	W	5.3	9.5	1.8	5.5	9.5	1.7	Cirr. of liver; edema of legs
15	22	F	C	5.9	4.1	3.1	F.U.O.
16	17	M	C	5.3	13.4	2.5	5.2	17.0	3.3	5.3	11.6	2.2	Pern. anemia
17	46	M	W	4.2	20.6	4.9	4.3	60.5	14.1	4.3	46.0	10.7	Diab. mellitus
18	40	F	C	6.9	29.6	4.3	4.4	12.9	2.9	5.8	11.6	2.0	PID with psychoneurosis
19	..	F	C	13.5	57.7	4.3	3.7	36.3	9.8	3.7	46.1	12.5	Senility
20	64	M	C	4.0	10.4	2.6	2.7	8.7	3.2	3.5	8.9	2.5	Ac. rheumatic fever
21	20	F	C	12.8	39.7	3.1	4.0	85.5	21.4	3.3	89.3	27.1	
Mean	7.2	33.7	4.9	4.3	32.8	7.1	4.1	32.0	9.0	
Max.	13.5	57.7	16.7	5.3	85.5	21.4	5.8	89.3	27.1	
Min.	2.9	10.4	2.5	2.7	9.5	1.8	1.3	8.9	1.7	

C = Comfortable environmental conditions. H. & H. = Hot and humid environmental conditions. H.H.:C = Ratio of rates in hot and humid environment to that in comfortable environment.

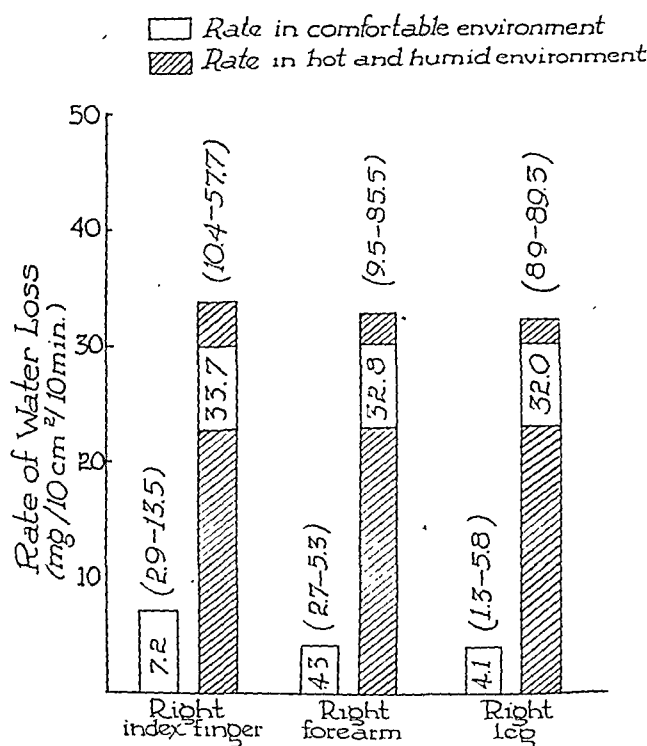


FIG. 2.—The rates of water loss in the patients with miscellaneous disease states other than congestive heart failure.

throbbing headaches, or sensations in the temporal regions, flushing of the face; a psychologic state of discomfort and unhappiness and annoyance. There was vertigo at times.

The patients with severe congestive heart failure complained most of discom-

fort from the hot and humid room. Three patients objected bitterly to the heat and humidity. They experienced a sense of marked suffocation and became restless, then very excited and very dyspneic, finally developing almost a state of panic. They were unable to remain in the room,

TABLE 3.—THE RATES OF WATER LOSS IN PATIENTS WITH MILD, MODERATE AND SEVERE RIGHT AND LEFT VENTRICULAR CONGESTIVE HEART FAILURE

Subject				Parts studied									State of failure
				Finger			Forearm			Leg			
No.	Age	Sex	Color	C	H. & H.	H.H.:C	C	H. & H.	H.H.:C	C	H. & H.	H.H.:C	
22	12	M	C	8.6	34.8	4.0	3.9	70.7	18.2	3.7	77.1	20.8	Slight to none
23	42	F	C	8.2	38.8	4.7	5.7	37.7	6.6	5.3	31.2	5.9	Slight to moderate
24	51	M	C	6.0	4.7	5.2	Slight to moderate
25	38	F	C	8.9	28.3	3.2	6.9	43.1	6.2	5.8	29.3	5.1	Slight
26	68	F	C	5.6	23.7	4.2	3.5	20.3	5.8	2.7	30.7	11.4	Slight to moderate
Mean	7.5	31.4	4.0	4.9	43.0	9.2	4.5	42.1	11.3	
Max.	8.9	38.8	4.7	6.9	70.7	18.2	5.8	77.1	20.8	
Min.	5.6	23.7	3.2	3.5	20.3	5.8	2.7	29.3	5.1	
27	43	F	C	11.3	20.2	1.8	7.9	36.3	4.6	9.4	23.7	2.5	Moderate
28	36	F	W	7.6	20.0	2.6	9.4	21.2	2.3	12.7	35.2	2.8	Moderate
29	42	M	C	4.6	4.4	5.0	Moderate
30	52	M	C	6.7	15.4	2.3	4.0	24.4	6.1	3.3	12.1	8.7	Moderate to severe
31	28	F	C	5.2	17.5	3.4	6.9	16.1	2.3	6.0	22.8	3.8	Moderate
32	46	M	C	7.5	15.7	2.1	4.1	21.1	5.1	4.5	27.3	6.1	Moderate
Mean	7.2	17.7	2.4	6.1	23.8	4.1	6.8	24.2	3.8	
Max.	11.3	20.2	3.4	9.4	36.3	6.1	12.7	35.2	6.1	
Min.	4.8	15.4	1.8	4.0	16.1	2.3	3.3	12.1	2.5	
33	65	M	C	6.0	12.2	2.0	5.2	8.8	1.7	4.5	7.9	1.8	Severe
34	51	M	C	3.8	10.6	2.8	5.2	9.3	1.8	4.1	9.9	2.4	Severe
35	53	F	C	6.2	17.4	2.8	5.7	10.0	1.8	3.6	8.9	2.5	Severe
36	62	M	W	4.2	14.0	3.3	6.0	15.5	2.6	6.3	19.1	3.0	Severe
37	67	M	C	3.8	13.3	3.5	4.7	12.8	2.7	4.4	12.5	2.8	Severe
38	30	M	C	5.4	11.9	2.2	4.0	12.0	3.0	5.7	10.0	1.8	Severe
39	60	F	C	4.4	11.5	2.6	1.6	7.5	4.7	1.9	6.7	3.5	Severe
40	43	F	C	8.1	15.1	1.9	7.2	14.0	1.9	5.1	16.4	3.2	Severe
41	52	F	C	5.1	12.6	2.5	5.7	9.6	1.7	5.1	8.8	1.7	Severe
42	53	F	C	7.0	13.1	1.9	3.3	8.0	2.4	3.6	7.5	2.1	Severe
Mean	5.4	13.2	2.6	4.9	10.8	2.4	4.4	10.8	2.5	
Max.	8.1	17.4	3.5	7.2	15.5	4.7	6.3	19.1	3.5	
Min.	3.8	10.6	1.9	1.6	7.5	1.7	1.9	6.7	1.7	

C = Comfortable environmental conditions. H. & H. = Hot and humid environmental conditions. H.H.:C = Ratio of rates in hot and humid environment to that in comfortable environment.

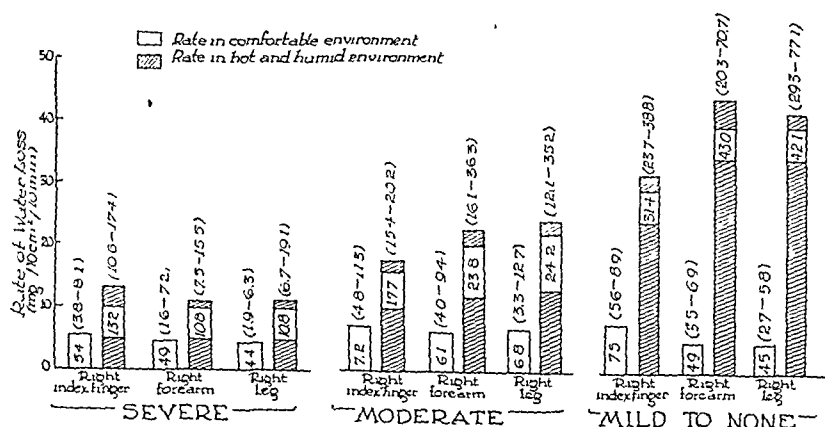


FIG. 3.—The rate of water loss in patients with various degrees of congestive heart failure. The rate of water loss in the hot and humid environment approaches normal as the heart compensates.

making it impossible to conduct the measurements. The syndrome precipitated by the hot and humid air, resembled an acute episode of cardiac asthma. Several days later, after their congestive failure had subsided, they were able to withstand the hot and humid atmosphere and the studies were completed. It was noted that this extreme and rather dramatic reaction to the hot and humid atmosphere was particularly marked if patients were suddenly wheeled into the hot room instead of being allowed to remain in bed while the room conditions were changed

body during heart failure or another expression of disturbance in water distribution in heart failure is also unknown. Nevertheless, this reduction in sweating in a hot and humid atmosphere does result in an impairment in thermal regulation. Sensible perspiration is concerned mainly with emergency heat elimination whenever the thermal equilibrium is upset by rapid heat production or the conditions of the environment or the circulation interferes with heat loss by radiation, conduction, and convection. In congestive heart failure, there is an increase in heat

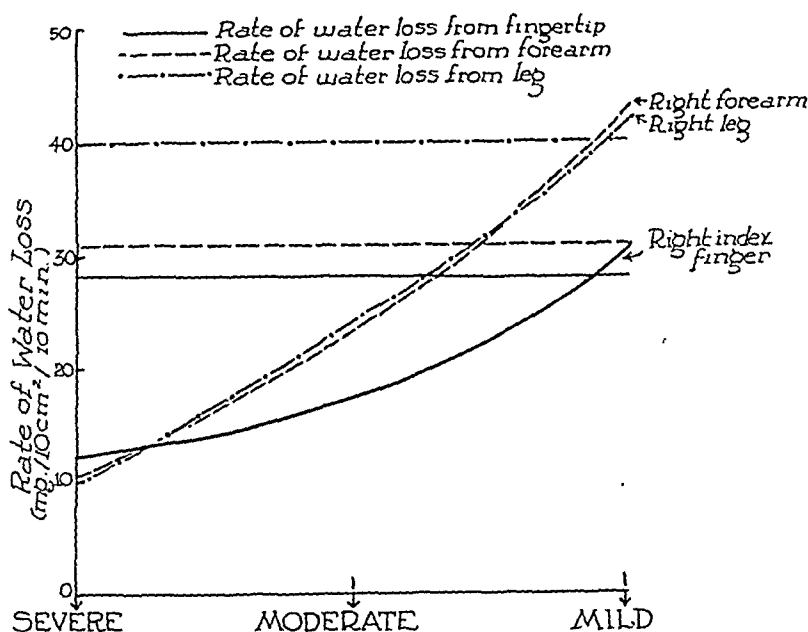


FIG. 4.—Relation of the rates of water loss in patients with various degrees of congestive heart failure to that in the normal subjects.

from a comfortable one to a hot and humid one over a period of 15 to 20 minutes.

Under hot and humid environmental conditions, the rate of water loss from the skin of patients with severe congestive heart failure is considerably less than normal. The rate also tends to be slightly less under conditions of a comfortable environment. The mechanism for these differences is unknown. Whether or not this is a compensating mechanism designed to assist in the maintenance of a normal state of water equilibrium throughout the

production because of the exertion and anxiety. In addition, the impairment of the circulation with 'venous stasis' results in impairment of heat loss by conduction, radiation and convection. The heat produced in the muscles and viscera internally cannot be efficiently transported by the blood to the surface of the body for elimination. Therefore, under such physiologic conditions heat loss by vaporization of water from the surface of the body becomes important. From the data presented, heat loss by sweating is also impaired. It is obvious, then, that patients

with congestive heart failure should be more comfortable in a cool atmosphere. This was found to be true by clinical observations. Although, because of the lack of facilities, no observations were conducted to learn the influence of the temperature and humidity of the environment upon the recuperative processes in congestive heart failure, the above acute experiments make it possible to conclude safely that a cool atmosphere is to be insisted upon in the proper management of congestive heart failure. In fact, the results make it imperative to avoid hot and humid room conditions in its treatment.

Steele and Cohn^{3,9,10} attributed the fever encountered in congestive heart failure to the impairment of the circulation *per se* with a resultant impairment of heat loss by radiation, conduction and convection. This is certainly a significant factor concerned with this type of fever, particularly when the patients are in a cool and comfortable environment. As shown above, the impairment of the sweating mechanism also contributes to the abnormal elevation in body temperature in congestive heart failure. With a marked impairment of the emergency sweating mechanism, heat loss in a hot and humid atmosphere is particularly disturbed, thus predisposing even more to the accumulation of body heat.

None of the normal or diseased subjects studied, enjoyed the hot and humid atmosphere. The patients with severe congestive heart failure and impairment of sweating suffered greatest subjectively in the hot and humid atmosphere. The subjects who perspired normally suffered less. That a seizure or an acute exacerbation of congestive heart failure was or would be precipitated by a hot and humid environment is not surprising when the rôle of the cardiovascular system in heat elimination is considered. The acute demands placed upon the cardiovascular system, and the heart in particular, by an acute need for a marked increase in heat elimination may be considerable. There is a

sudden increase in heart rate and cardiac output per minute with an associated diffuse vasodilatation. Such physiologic phenomena certainly exert deleterious influences on an already failing heart, resulting in an acute exacerbation of an already existing congestive heart failure or precipitating impending failure.

When dealing with a physiologic state as complicated as congestive heart failure, it is impossible under the conditions of the observations described above to evaluate the nature of the rôle of impaired sweating in the discomfort experienced by the patients with congestive heart failure. It is certainly probable that the reduced rate of heat loss by the evaporation of sweat must play a significant rôle in the patient's discomfort when in the hot, humid atmosphere.

The results of water loss in the patients with mild and moderate congestive heart failure show a return to normal of this physiologic mechanism as the cardiac function returns to normal. This is particularly well illustrated by Figure 4.

These studies indicate the great importance of considering the conditions of the environmental temperature when treating patients with congestive heart failure. This, obviously, is particularly important in subtropical and tropical climates. More attention should be given to the use of air-conditioning of hospitals. Air-conditioning of operating rooms is fairly common, but little attention is directed to air-conditioning of medical wards, especially those containing patients with congestive heart failure. The monographs on congestive heart failure contain little or nothing concerning the problem of room atmospheric conditions in the discussions of the management of congestive heart failure,^{4,5,11} although a single statement by Harrison⁵ ("the temperature of the room should not be allowed to become excessive during the night because heat may precipitate a seizure" [of cardiac asthma]) was encountered.

The ratios of the rates of water loss in the hot and humid environments show

that less sweating occurs for the finger tip than the limbs of the body (Tables 1 and 2). For example, in the normal the ratio for the mean rates for the tip of the finger was 2.8 (extremes 1.5 and 4.8), while for the forearm and leg the mean ratios were 5.9 (extremes 1.5 and 9.4) and 8 (extremes 1.9 and 12.9) respectively. Other data (unpublished) from this laboratory, showed that there is relatively little increase in the rate of sweating when a subject enters a hot and humid environment. These results indicate a lack of response of the sweat glands of the skin of the palms (soles as well) to a general stimulus for emergency sweating to eliminate heat by vaporization. Sweating from the palmar and plantar skin areas is, therefore, not concerned very much with heat elimination. Marked sweating initiated by psychogenic factors is well known for these areas. As indicated above, in severe congestive heart failure the sweat glands in general as well as the palmar skin fail to secrete appreciably to meet the demands of emergency heat elimination.

Summary. 1. The rate of water loss from the skin of three widely separated areas of the body (finger tip, forearm and leg), studied simultaneously, showed a marked impairment of sweating in patients with severe (Class IV) congestive heart failure resting in a hot and humid environment. Under these conditions, the mean rates of water loss varied between 27 and 47% of that in normal subjects under similar environmental conditions.

2. As the congestive heart failure subsided, the rate of water loss or sweating in hot and humid atmospheric conditions returned to normal, reaching normal rates when the failure became nil or disappeared.

3. The mean rate of water loss in a group of patients suffering from disease states other than congestive failure was normal.

4. The hot and humid room atmosphere produced more discomfort in the patients with severe congestive heart failure than in those without failure or only mild failure. In 3 instances, seizures of cardiac asthma with the associated anxiety and almost panic were precipitated by the hot and humid environment.

Conclusions. 1. The importance of ensuring a cool and comfortable atmosphere in order to avoid any unnecessary excitation of the thermal regulatory mechanism is emphasized in the therapeutic management of congestive heart failure. It is well to remember that conditions of the environment which result in a stimulation of the physiologic processes concerned with heat elimination result in an excitation of the cardiovascular mechanisms. The cardiovascular system is greatly involved in heat elimination especially when heat loss by sweating is impaired. During congestive heart failure, the cardiovascular system should have only a minimum demand placed upon it.

2. A greater need for air-conditioning in medical wards containing patients with heart disease is emphasized. This is particularly important in subtropical and tropical climates.

The author wishes to express his appreciation to Mr. G. Morgavi for his keen interest and significant technical assistance in these studies.

REFERENCES

1. BURCH, G. E., COHN, A. E., and NEUMANN, C.: A Study of the Total Volume of the Human Finger Tip and Toe Tip, *Human Biol.*, **13**, 526, 1941.
2. BURCH, G. E., and SODEMAN, W. A.: Regional Relationships of Rate of Water Loss in Normal Adults in a Subtropical Climate, *Am. J. Physiol.*, **138**, 603, 1943.
3. COHN, A. E., and STEELE, J.: Unexplained Fever in Heart Failure, *J. Clin. Invest.*, **13**, 853, 1934.
4. FISHBERG, A. M.: *Heart Failure*, 2nd ed., Phila., Lea & Febiger, 1940.
5. HARRISON, T. R.: *Failure of the Circulation*, Balt., Williams & Wilkins, 1939.
6. ISBELL, H.: The Human Finger Tip: Surface Area and Volume Correlations, *Human Biol.*, **11**, 536, 1939.
7. KINSEY, D., and WHITE, P. D.: Fever in Congestive Heart Failure, *Arch. Int. Med.*, **65**, 163, 1940.
8. NEUMANN, C., COHN, A. E., and BURCH, G. E.: A Quantitative Method for the Measurement of the Rate of Water Loss From Small Areas, etc., *Am. J. Physiol.*, **132**, 748, 1941.
9. STEELE, J.: Fever in Heart Disease, *Internat. Clin.*, **1**, 17, 1936.
10. STEELE, J., and COHN, A. E.: Fever in Heart Failure; Relation Between Temperatures of Interior and Surface of Body, *J. Clin. Invest.*, **13**, 869, 1934.
11. WHITE, P. D.: *Heart Disease*, 3d ed., New York, Macmillan, 1944.

THE RESPIRATORY QUOTIENT AND BLOOD PYRUVATE AND LACTATE RESPONSES AFTER ORAL INGESTION OF GLUCOSE AND FRUCTOSE IN DIABETES MELLITUS WITH AND WITHOUT INSULIN

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THE abnormally low respiratory quotient (R.Q.) observed in diabetes and the failure to observe a rise in R.Q. in diabetic animals and man after glucose administration as contrasted to the positive response observed in normal animals and human subjects^{7,12,14} have been principal arguments for the belief that glucose is not adequately oxidized in diabetes. This evidence for "under-utilization" of sugar in diabetes has been assailed, particularly by Soskin,¹⁵ and his comments are partially justified in that other metabolic transformations could also contribute to or account for the lowered R.Q. noted in diabetes. It was evident that another indicator of the intensity of carbohydrate oxidation was required to substantiate the interpretations of the R.Q. measurements. The carbohydrate intermediate pyruvic acid (PA) and its reduction product (LA) are readily measured in the blood, and their measurement offers a means of estimating the intensity of an intermediate stage of carbohydrate metabolism.

Perhaps the most significant recent contribution to an understanding of the biochemical defect in diabetes is the finding of a negative PA response to glucose administration. Bueding, Stein, and Wortis³ noted an average rise in blood PA of 0.46 mg. % (from approximately 1 mg. %) at the end of 1 hour after the ingestion of 1.75 gm. of glucose per kg. of body weight. Both Bueding and coworkers⁴ and Klein¹³ showed however that such a response was

absent in diabetic patients unless insulin was also administered. These findings were even more clearly demonstrated with depancreatized dogs⁶ and have led to the conclusion that insulin is concerned in the formation of pyruvate from glucose. Chesler and Himwich⁹ have shown that the ratio between PA and LA underwent only slight fluctuations as the result of injection of insulin into depancreatized dogs.

This paper presents simultaneous measurements of R.Q. with blood sugar, PA, and LA changes after the administration of 50 gm. of glucose or fructose, with or without insulin, to diabetic subjects. A negative response in R.Q. was nearly invariably accompanied by a negative response of PA and LA, but when a significant rise in R.Q. was obtained, particularly as a result of previous insulin administration, PA and LA also increased. The findings confirm earlier results on the PA response to glucose and support the contention that the negative R.Q. response to glucose in diabetes indicates a decreased oxidation of carbohydrate.

Procedure and Methods. The respiratory exchange* was measured with an open-circuit helmet apparatus² and gas-analysis apparatus.⁸ The latter was standardized each day prior to the metabolism test by analyses of samples of outdoor air. The patient, without breakfast, came to the metabolism laboratory between 8 and 9 A.M. and lay quietly in bed for 30 minutes. The helmet was then put over the head, the patient

* The respiratory exchange measurements and the gas analyses were made by Miss Jeannette F. Rayner.

was connected with the respiration apparatus, and after a 15-minute preliminary period the basal metabolism was measured in 3 consecutive 10 minute periods. The helmet was then removed, and the patient drank the sugar solution, usually in about 1 minute. The solution consisted of 50 gm. of glucose or fructose dissolved in 300 cc. of water, and an additional 50 cc. of water was used for a rinse. The temperature of the dose ranged from 15 to 20° C. One hour after the ingestion of glucose and 30 minutes after ingestion of fructose, the metabolism measurements were continued for five 10 minute periods. These were not all consecutive but were grouped in series of 2, 2 and 1 each, with a 15 minute pause after each series during which time the helmet was removed from the patient's head.

Samples of blood were taken from the basilic vein, with care taken to remove tourniquet to avoid stasis, at the end of the basal measurements and 30, 60, 90 and 120 minutes after ingestion of the sugar. The blood samples were analyzed for blood sugar by the method of Folin,¹¹ PA according to Bueding and Wortis⁶ and LA by the colorimetric method of Barker and Summerson.¹ Blood for PA analysis was drawn and preserved with the special precautions against loss advised by Bueding and Wortis (above).

In 26 tests with glucose and 13 tests with fructose the patients received no insulin along with the sugar and, in fact, had been without insulin for varying lengths of time prior to the tests, as indicated in the Tables. In 20 tests with glucose and 2 tests with fructose, crystalline insulin (solution of zinc insulin crystals) was given subcutaneously immediately before or after the patient drank the sugar solution. The amount given varied according to the needs of the patient.

Results. Clinical Data. In Tables 1 and 2 are reported the clinical data regarding the patients, including age of patient and duration of disease, information concerning the insulin treatment on the day before the metabolism test, explanatory remarks about the duration of the diabetes and any accompanying complications. The patients are divided into four main groups, those who received glucose without and with simultaneous administration of insulin, and those who received fructose

without and with simultaneous administration of insulin. In these groups there are subdivisions of the patients as follows: (1) those who had not been taking insulin at all; (2) those who had not received insulin for over 24 hours, that is, who had taken no insulin on the day before the test; (3) those who had been without insulin for 24 hours, that is, who had had insulin at 7 or 8 A.M. on the day preceding the test; (4) those who had had insulin within 12 to 20 hours before the test; and (5) those who had had insulin within 1 to 2 hours before the test.

Tables 1 and 2 show that 5 patients had had the disease less than 1 year, 12 patients had had the disease 1 to 5 years, 14 patients, between 5 and 10 years, leaving 4 patients who had the disease more than 10 years. Nine patients were under 20 years of age, 22 were between 20 and 50 years of age, and 9 were over 50 years of age.

Glucose Without Insulin. In Table 3 are reported the results of the measurements on the patients who were given orally 50 gm. of glucose without simultaneous injection of insulin. Among the patients who had not been taking insulin at all or had not received insulin for over 24 hours, there are 4 (Nos. 37, 35, 4 and 8) who showed definite increases in the R.Q. above the basal level after ingestion of the glucose. Of these, 2 (Nos. 37 and 4) also showed definite increases in the PA and the LA content of the blood. No. 35 showed small increases in the PA at 1½ and 2 hours after ingestion and a very slight increase in the LA at 1½ hours. No. 8 had no significant increases in either PA or LA.

The group of patients who had received insulin at 7 or 8 A.M. on the day preceding the test have been divided into two subgroups, those who had a definite rise in R.Q. in all or in some of the periods following the ingestion of glucose and those who had no rise or else a fall in R.Q. after the glucose. In the first of these subgroups, all 5 patients had rises in R.Q. in at least one series of periods, and 3 of

TABLE 1.—CLINICAL DATA REGARDING DIABETIC PATIENTS WHO RECEIVED 50 GRAMS OF DEXTROSE BY MOUTH

Type of test and case no.	Age of patient (yrs.)	Duration of disease	Insulin on day before test			Remarks
			Crystalline (units)	Protamine zinc (units)		
				Time given		
50 GRAMS OF DEXTROSE						
Without Insulin 24 Hours Before Test						
1	28	4 yrs.	..	24	7.00 A.M.	
2	59	6 "	24	56	8.00 A.M.	Insulin resistant
3	20	3 "	250	..	6.10 A.M.	Coma on preceding day
4	26	5 mos.	0	0	...	Mild diabetes; takes no insulin
5	59	7 yrs.	8	28	8.00 A.M.	
6	48	10 "	0	0	...	Takes no insulin
7	42	4 "	24	48	7.00 A.M.	Acidosis 4 days previous
8	56	2 "	0	0	...	Thyroidectomy 2 mos. previous; takes no insulin; remission of diabetes
9	19	3 wks.				
10	16	2 "	24	48	7.00 A.M.	
11	43	10 yrs.	120	..	8.10 A.M.	
12	35	17 "	8	32	8.00 A.M.	Unstable; highly sensitive to insulin
13	13	30	..	New diabetic
Without Insulin 12 to 20 Hours Before Test						
14	16	5 yrs. +	16	44	7.30 A.M.	Coma 4 days previous
			8	..	12.30 P.M.	
			8	..	4.30 P.M.	
15	35	8 "	10	..	4.30 P.M.	
16	47	1 yr.	24	48	8.00 A.M.	
			10	..	11.30 A.M.	
17	16	16	9.00 P.M.	New diabetic; has had insulin only once
18	26	7 yrs.	20	36	7.00 A.M.	
			10	..	12 NOON	
19	62	21 "	650	..	9.30 A.M.	Areas of fatty atrophy; insulin resistant
			550	..	12.30 P.M.	
			500	..	5.30 P.M.	
			150	..	9.00 P.M.	
20	38	7 "	60	..	6.30 A.M.	Acidosis day before test
			24	..	10.00 A.M.	
			8	..	2.00 P.M.	
			8	..	6.00 P.M.	
21	31	5 "	24	40	7.00 A.M.	Insulin resistant
			10	..	12 NOON	
			10	..	5.00 P.M.	
22	20	13 yrs.	16	..	5.00 P.M.	Dwarf; adm. to hosp. on previous day; prob. had insulin at home before admission
23	56	7 "	30	50	7.00 A.M.	Coma 5 days previous
			12	..	12 NOON	
			12	..	5.00 P.M.	
50 GRAMS OF DEXTROSE + INSULIN						
Without Insulin 24 Hours Before Test						
2	59	6 yrs.	20	48	8.00 A.M.	Insulin resistant
24	57	4 "	..	24	8.15 A.M.	Adenoma of thyroid
10	16	2 wks.	20	40	7.00 A.M.	
17	16	..	16	36	7.00 A.M.	
25	53	8 yrs.	6	20	8.00 A.M.	
4	26	5 mos.	0	0	...	Mild diabetes
26	52	3 yrs.	16	36	9.15 A.M.	Acidosis on 3 prec. days; possible B ₁ defic. may explain rise in PA and LA of blood
27	17	2 "	50	50	7.00 A.M.	
28	72	3 "	12	44	7.00 A.M.	Coma 10 days before test
Without Insulin 15 to 20 Hours Before Test						
29	31	..	20	40	1.30 P.M.	Coma on preceding day
22	20	13 yrs.	18	48	7.00 A.M.	
			6	..	12 NOON	
			4	..	5.00 P.M.	
3	20	3 "	26	50	7.00 A.M.	Coma 6 days before
			8	..	5.00 P.M.	
30	47	11 "	..	24	12.30 P.M.	Pituitary tumor and hypopituitarism
19	62	21 "	600	..	8.30 A.M.	Insulin resistant
			500	..	12.30 P.M.	
			450	..	3.30 P.M.	
11	43	10 "	120	..	12.30 P.M.	Insulin resistant
			40	..	5.00 P.M.	
31	45	2 mos.	18	36	7.30 A.M.	
			6	..	12 NOON	
20	38	7 yrs.	30	36	7.00 A.M.	Acidosis 9 days previous
			6	..	5.00 P.M.	
32	27	6 "	..	8	7.30 A.M.	
			10	..	12 NOON	
			10	..	5.00 P.M.	
No Insulin Taken on Day Before Test						
33	15	1 mo.	0	0	...	Goiter; insulin reaction after test
34	40	9 yrs.	0	0	...	
35	47	1 yr. +	0	0	...	
36	34	2 yrs.	0	0	...	
50 GRAMS OF DEXTROSE						
Takes No Insulin						
37	17	...	0	0	...	Diabetes and renal glycosuria

TABLE 2.—CLINICAL DATA REGARDING DIABETIC PATIENTS WHO RECEIVED 50 GRAMS OF FRUCTOSE:
Insulin on day before test

Type of test and case no.	Age of patient (yrs.)	Duration of disease	Crystalline (units)	Protamine zinc (units)	Time given	Remarks
50 GRAMS OF FRUCTOSE						
Without Insulin 2½ Hours Before Test						
15	35	8 yrs.	20	66	8.30 A.M.	
36	34	2 "	6	24	7.00 A.M.	New diabetic
30	47	11 "	6	28	7.00 A.M.	Pituitary tumor; has taken 6 gr. thyroid extract for past 3 days
7	42	4 "	24	56	7.00 A.M.	Coma 6 days previous; took cup of black coffee before test
Without Insulin 12 to 20 Hours Before Test						
1	28	4 yrs.	..	20	12.30 P.M.	
35	47	1 yr. +	..	20	12.30 P.M.	
38	49	6 yrs.	14	30	8.00 A.M.	
			4	..	4.30 P.M.	
13	13	..	16	32	12.30 P.M.	
			4	..	5.00 P.M.	
12	35	17 yrs.	12	28	8.00 A.M.	Unstable; highly sensitive to insulin
			8	..	4.30 P.M.	
Insulin 1 to 2 Hours Before Test						
14	16	5 yrs. +	20	50	7.15 A.M.	Coma 6 days previous
			4	..	12 NOON	
21	31	5 "	50	80	7.00 A.M.	Insulin resistant
			6	..	12 NOON	
16	47	1 yr.	24	48	12 NOON	
			8	..	4.30 P.M.	
39	18	7 yrs.	20	44	7.00 A.M.	
			6	..	12 NOON	
			6	..	5.00 P.M.	
50 GRAMS OF FRUCTOSE + INSULIN						
29	31	..	20	40	12 NOON	Coma 2 days previous
			10	..	5.00 P.M.	
25	53	8 yrs.	..	20	8.00 A.M.	

TABLE 3.—CHANGES FROM BASE-LINE IN RESPIRATORY QUOTIENT, AND SUGAR, PYRUVIC ACID AND LACTIC ACID OF BLOOD OF DIABETIC PATIENTS AFTER INGESTION OF 50 GRAMS OF DEXTROSE

Condition and case no.	Respiratory quotient				Blood sugar (mg. per 100 cc.)				Pyruvic acid (mg. per 100 cc.)				Lactic acid (mg. per 100 cc.)			
	Changes from basal after dextrose				Changes from basal after dextrose				Changes from basal after dextrose				Changes from basal after dextrose			
	Basal	1-1½ hrs.	1½-2 hrs.	2-2½ hrs.	Basal	½ hr.	1½ hrs.	2 hrs.	Basal	½ hr.	1½ hrs.	2 hrs.	Basal	½ hr.	1½ hrs.	2 hrs.
TAKES NO INSULIN (MILD OR BORDERLINE DIABETES)																
37	0.81	+0.09	+0.09	+0.12	62	+54	+12	+27	1.4	+0.2	+0.4	+0.2	8.8	+1.6	+4.0	+3.7
4	0.82	+0.03	+0.06	+0.04	112	+63	+123	+144	1.5	+0.4	+0.6	+0.3	12.2	+4.2	+6.6	+4.1
6	0.88	0.00	+0.01	+0.01	54	+51	+72	+107	1.3	+0.1	+0.1	+0.1	6.4	+0.2	+0.2	-0.2
8	0.84	+0.11	+0.09	+0.03	106	+34	+81	+14	1.4	0.0	0.0	0.0	8.8	+0.2	+0.3	+0.3
NO INSULIN TAKEN ON DAY BEFORE TEST																
35	0.77	+0.05	+0.07	+0.04	122	+95	+145	+113	1.0	0.0	+0.2	+0.2	7.0	+0.2	+0.6	+0.2
36	0.82	-0.01	-0.01	-0.01	89	+43	+167	+189	1.0	+0.1	0.0	0.0	6.2	+0.4	+0.2	+0.2
WITHOUT INSULIN 24 HOURS BEFORE TEST																
1	0.81	+0.01	+0.03	+0.01	77	+33	+82	..*	1.2	0.0	0.0	..*	6.7	0.0	0.0	*
2	0.77	+0.02	+0.02	+0.05	163	+57	+111	+104	1.3	0.0	+0.1	0.0	8.0	0.0	+0.1	0.0
3	0.75	0.0	+0.03	+0.04	70	+17	+130	+147	1.1	0.0	0.0	-0.1				
5	0.82	+0.07	+0.07	+0.11	157	+32	+133	+146	1.3	0.0	+0.2	+0.3	8.8	+0.4	+1.8	+2.7
7	0.80	+0.04	+0.06	+0.05	177	+90	..	+187	1.2	+0.1	+0.1	+0.1	6.8	+0.1	+0.1	-0.1
10	0.89	-0.02	-0.03	-0.01	59	+1	+32	+85	1.2	0.0	0.0	+0.1	6.4	0.0	+0.1	+0.2
9	0.84	-0.03	-0.03	-0.04	87	+16	+103	+130	1.3	0.0	+0.2	+0.2	8.6	-0.1	+2.3	+2.4
13	0.80	-0.01	-0.02	-0.01	151	+36	+105	+148	1.2	+0.1	0.0	+0.1	8.7	+0.7	+0.3	+0.3
11	0.79	0.00	-0.01	+0.02	274	+59	+142	+170	1.0	-0.1	-0.1	-0.2	7.5	-0.9	-1.6	-1.6
12	0.76	0.00	-0.03	-0.04	206	+102	+182	+132	1.5	0.0	+0.1	0.0	9.2	0.0	+0.2	0.0
WITHOUT INSULIN 12 TO 20 HOURS BEFORE TEST																
14	0.85	+0.01	-0.03	+0.05	160	+114	+198	+210	1.2	+0.1	0.0	0.0	8.6	+1.4	+0.3	+0.3
15	0.72	+0.04	+0.07	+0.05	215	+18	+155	+149	1.3	0.0	-0.1	0.0	9.6	+0.3	-0.4	-0.2
16	0.79	+0.03	+0.02	+0.01	256	+47	+124	+144	1.3	0.0	0.0	0.0	9.0	0.0	+0.1	+0.1
17	0.74	+0.02	+0.03	+0.02	267	+97	+177	+93	2.2	-0.2	+0.1	0.0	13.2	-2.2	-0.2	-0.5
18	0.74	+0.02	+0.09	+0.10	220	+1	+21	+24	1.2	+0.1	+0.3	+0.5	6.8	+0.6	+2.6	+3.5
19	0.77	+0.02	+0.03	..	111	+175	+247	+222	1.2	0.0	0.0	0.0				
20	0.74	+0.05	+0.04	+0.03	57	+187	+50	+141	1.1	0.0	0.0	0.0	6.8	0.0	-0.1	+0.1
21	0.74	-0.01	-0.02	0.00	196	+31	+98	+12	1.4	0.0	+0.1	0.0	8.8	+0.2	+0.8	+0.4
22	0.77	-0.02	-0.01	-0.01	145	+72	+178	+193	1.4	-0.2	-0.1	-0.1	8.6	-0.6	-0.2	-0.2
23	0.77	-0.02	-0.02	..	175	+78	+107	+92	1.3	0.0	+0.1	-0.1	10.6	0.0	-0.1	-0.4

* The changes in the blood values 2½ hrs. after dextrose were +105, 0.0 and +0.1 respectively.

them (Nos. 2, 5 and 7) had definite rises in R.Q. in all the measurements. However, there were significant rises in PA and LA with only one of these patients (No. 5), at $1\frac{1}{2}$ and 2 hours after ingestion of glucose. This patient also had the most marked rises in R.Q. From the data for this subgroup it can be concluded that increases in R.Q. after glucose may amount to 0.06 without any significant change in either PA or LA of the blood. In the other subgroup, that is, patients who showed either a fall in R.Q. or no marked change, there were significant increases in PA and LA at $1\frac{1}{2}$ and 2 hours with No. 9. The only explanation that can be given for this fall in R.Q. accompanied by increases in the blood acids is that the basal R.Q. may have been too high because of nervous apprehension during the basal period and hence the true changes in R.Q. are not shown. The remainder of the data for this subgroup are consistent in that, with no rise or a fall in R.Q., there was no significant rise or else a fall in the PA and LA of the blood.

The group of patients who had not received insulin within 12 to 20 hours before the tests were made is also divided into subgroups, that is, those who showed a definite rise in R.Q. at some period after the ingestion of glucose and those who did not. In the first subgroup there are 2 patients (Nos. 15 and 20) who had definite rises in R.Q. in all the periods after glucose and yet showed no increase in either PA or LA in any of the blood samples. The rises in R.Q. of No. 15 are of such an order of magnitude that one would expect a rise in PA and LA if there is a relationship between changes in R.Q. and changes in these acids, and yet the rises in the blood acids are only slight. The first R.Q. of No. 20 after glucose also underwent a marked rise. With No. 18 there was a marked rise in R.Q. and PA and LA at $1\frac{1}{2}$ to 2 hours and at 2 to $2\frac{1}{2}$ hours. In none of the other periods were there any significant increases in either PA or LA when there were rises in R.Q. None of the rises in R.Q. except those already

noted were large. In the second subgroup the data are thoroughly consistent in that with no rise or a fall in R.Q. there was no increase in the PA and LA of the blood.

Practically none who had had coma or acidosis recently or were classified as insulin resistant gave any marked rises in R.Q., PA, and LA.

In general, patients with diabetes may show slight rises in R.Q. after ingestion of 50 gm. of glucose without significant increases in the PA and LA of the blood, but when the rises in R.Q. are over 0.05, these are likely to be accompanied by significant increases in the PA and the LA of the blood.

Glucose With Simultaneous Injection of Insulin. Twenty patients were given 50 gm. of glucose together with subcutaneous injection of insulin in various amounts. The results of the measurements are shown in Table 4.

The 3 patients to whom no insulin was given on the day before the tests all showed definite rises in R.Q. The rises with Nos. 31 and 34 were somewhat larger than would be obtained if normal persons were given glucose alone, so that insulin brought about a larger increase in R.Q. than normally occurs. The insulin dosage was large enough so that there was a marked fall in the blood sugar with 2 patients instead of a rise that might occur after glucose alone. One patient (No. 33) had definite increases in the PA and LA at all 3 times of measurement. No. 34 gave a rise in PA and LA at $1\frac{1}{2}$ and 2 hours after glucose. The third patient (No. 4) had a significant rise only in the LA, at $1\frac{1}{2}$ and 2 hours.

Of the patients to whom insulin was given at 7 or 8 A.M. on the day preceding the test, all showed rises in R.Q. in all the periods except the first with No. 27. The rises in R.Q. with Nos. 28, 10 and 26, were large and greater than would occur, on the average, in normals with glucose alone. These 3 patients also showed increases in both PA and LA at $1\frac{1}{2}$ and 2 hours. With the exception of Nos. 27 and 24, all patients showed rises in LA at $1\frac{1}{2}$ and 2

hours, and the same is true for the most part with PA.

Of the patients who received no insulin within 15 to 20 hours before the tests, 3 (Nos. 31, 20 and 32) had marked rises in R.Q., particularly in the second and third periods, and the rises were accompanied by rises in PA and LA. With Nos. 22 and 3 there were small or no rises in R.Q., PA, and LA. No. 30 had large rises in R.Q. but little or no rise in the acids until the 2 hour period.

followed by large rises in R.Q., indeed much larger in some patients than would occur normally with healthy persons after glucose alone. In many instances there were large increases in both PA and LA, particularly in the latter. The increases in LA were with some patients larger than with normals after 100 gm. of glucose. Edwards and others¹⁰ found that with normal men ingestion of 100 gm. of glucose caused an increase in LA of 3 to 4 mg. per 100 cc. of blood at 45 minutes after

TABLE 4.—CHANGES FROM BASE-LINE IN RESPIRATORY QUOTIENT AND SUGAR, PYRUVIC ACID AND LACTIC ACID OF BLOOD OF DIABETIC PATIENTS AFTER INGESTION OF 50 GRAMS OF DEXTROSE AND SIMULTANEOUS ADMINISTRATION OF INSULIN

Con- dition and case no.	Insulin (un.)	Respiratory quotient				Blood sugar (mg. per 100 cc.)				Pyruvic acid (mg. per 100 cc.)				Lactic acid (mg. per 100 cc.)			
		Changes from basal after dextrose and insulin				Changes from basal after dextrose and insulin				Changes from basal after dextrose and insulin				Changes from basal after dextrose and insulin			
		1-1½ hrs. 1½-2 hrs. 2-2½ hrs.				½ hr. 1½ hrs. 2 hrs.				½ hr. 1½ hrs. 2 hrs.				½ hr. 1½ hrs. 2 hrs.			
		Basal	hrs.	hrs.	hrs.	Basal	hr.	hrs.	hrs.	Basal	hr.	hrs.	hrs.	Basal	hr.	hrs.	hrs.
No INSULIN TAKEN ON DAY BEFORE TEST																	
33	20	0.73	+0.13	+0.13	+0.21	183	- 35	- 40	-121	1.7	+0.2	+0.3	+0.6	8.8	+1.4	+ 5.7	+ 8.2
34	20	0.71	+0.16	+0.18	+0.16	364	- 10	- 36	- 78	1.5	+0.1	+1.2	+1.3	10.4	+0.4	+ 8.4	+ 8.6
4	10	0.82	+0.05	+0.07	+0.05	108	+ 29	+ 39	- 25	1.4	0.0	+0.1	+0.1	8.6	0.0	+ 2.8	+ 3.2
WITHOUT INSULIN FOR 24 HOURS BEFORE TEST																	
27	20	0.82	0.00	+0.03	+0.04	127	+ 95	+111	+ 88	1.2	-0.2	-0.2	-0.1	5.4	-0.4	- 0.1	- 0.1
28	24	0.79	+0.08	+0.13	+0.10	112	+ 90	+103	+ 99	1.2	+0.1	+0.4	+0.5	8.7	+0.5	+ 3.0	+ 3.7
2	30	0.79	+0.06	+0.05	+0.05	182	+ 71	+ 92	+ 68	1.5	0.0	+0.5	+0.4	8.3	+0.5	+ 2.9	+ 2.7
24	10	0.81	+0.05	+0.07	+0.07	119	+ 38	+125	+108	1.2	0.0	..	+0.1	6.6	+0.2	..	+ 0.3
10	20	0.94	+0.09	+0.10	+0.12	65	- 12	- 17	- 33*	1.2	+0.1	+0.2	+0.1*	6.5	+0.4	+ 1.6*	+ 1.5*
17	20	0.82	+0.06	+0.07	+0.07	126	+ 63	+109	+ 41	1.7	+0.1	+0.6	+0.7	10.5	+1.8	+ 8.5	+ 7.5
25	20	0.84	+0.10	44	+ 13	+ 24	..	1.5	-0.1	+0.1	..	11.2	-2.0	+ 0.4	..
26	20	0.79	+0.20	+0.16	+0.08	256	+ 22	+ 52	+ 14	0.7	0.0	+2.1	+2.2	3.8	+0.3	+19.9	+21.5
WITHOUT INSULIN 15 TO 20 HOURS BEFORE TEST																	
29	20	0.76	+0.03	+0.04	+0.02	199	+ 79	+113	+118	1.2	0.0	+0.6	+0.5	8.8	+0.2	+ 5.6	+ 5.8
22	20	0.80	0.0	+0.01	+0.03	105	+120	+162	+122	1.1	+0.1	+0.1	+0.2	6.9	+0.2	+ 0.5	+ 2.0
3	20	0.83	-0.01	+0.01	+0.04	103	+ 9	+ 89	+147	1.0	0.0	0.0	0.0	6.0	0.0	+ 0.1	0.0
30	16	0.78	+0.08	+0.09	+0.10	42	+ 37	+112	+103	1.4	+0.1	+0.1	+0.3	8.8	+0.5	+ 0.5	+ 1.9
19	300	0.77	+0.02	+0.13	..	80	+248†	..	+320	1.2	+1.1†	..	+0.3	6.8	+5.4†	..	+ 3.7
11	75	0.82	+0.01	+0.05	..	120	+ 78	+203	+210	1.1	-0.1	0.0	+0.2	7.0	-0.6	+ 1.3	+ 1.8
31	20	0.74	+0.18	+0.18	+0.18	127	+ 84	+ 93	+ 25	0.9	0.0	+0.7	+0.7	5.4	0.0	+ 5.3	+ 5.4
20	20	0.78	+0.06	+0.08	+0.12	112	+ 11	+ 31	+ 28	1.2	+0.1	+0.2	+0.3	8.0	+1.0	+ 1.8	+ 2.4
32	20	0.77	+0.05	+0.09	+0.10	129	+127	+147	+ 93	1.2	+0.2	+0.4	+0.5	7.4	+1.3	+ 3.6	+ 4.7

* The changes in the blood value 2½ hrs. after dextrose and insulin were -49, +0.2 and +2.5 mg. respectively. These values were obtained after the patient had had an insulin reaction.

† 67 minutes after dextrose and insulin.

Among the patients in Table 4, who had had recent coma or acidosis or were insulin resistant, 3 (Nos. 28, 26 and 20) gave marked rises in R.Q. All but No. 3 showed slight rises in PA and similarly all but No. 3 showed significant rises in LA even when the rise in R.Q. was low (0.06 or less).

In general, the ingestion of glucose and the simultaneous injection of insulin were

ingestion and of 1 to 3 mg. at 90 minutes. The effect of simultaneous injection of insulin along with oral ingestion of glucose is to bring about a larger increase in R.Q. in some patients than would occur in normals after glucose alone, a greater increase in LA than with normals, and a marked increase in PA at 1½ and 2 hours after ingestion. Therefore, part of the rise in R.Q. after insulin must be ascribed to

the effects of LA and PA in displacing carbon dioxide from the blood. Hence not all the rise in R.Q. can be ascribed to increased combustion of sugar, particularly when these rises are very large, but the largest effect of the acids would probably not be more than 0.03 to 0.04 on the R.Q.

In the group without insulin for 12 to 20 hours before the tests, patients Nos. 35 and 12 had large rises in R.Q. accompanied by definite increases in PA and LA, particularly No. 35. Patients Nos. 1 and 38 had little or no rise in R.Q. but did have significant increases in PA and LA. No. 13 had slight rises in R.Q. and significant

TABLE 5.—CHANGES FROM BASE-LINE IN RESPIRATORY QUOTIENT AND SUGAR, PYRUVIC ACID AND LACTIC ACID OF BLOOD OF DIABETIC PATIENTS AFTER INGESTION OF 50 GRAMS OF FRUCTOSE

Condition and case no.	Respiratory quotient				Blood sugar (mg. per 100 cc.)				Pyruvic acid (mg. per 100 cc.)				Lactic acid (mg. per 100 cc.)			
	Change from basal after fructose				Change from basal after fructose				Change from basal after fructose				Change from basal after fructose			
	Basal	½-1 hr.	1-1½ hrs.	1½-2 hrs.	Basal	½ hr.	1 hr.	2 hrs.	Basal	½ hr.	1 hr.	2 hrs.	Basal	½ hr.	1 hr.	2 hrs.
WITHOUT INSULIN FOR 24 HOURS BEFORE TEST																
15	0.81	+0.07	+0.12	+0.08	43	+63	+26	+58	1.3	0.0	+0.6	+0.8	9.0	0.0	+7.3	+8.2
36	0.82	+0.02	-0.01	-0.02	70	..	+71*	+72	1.2	..	0.0*	+0.1	6.6	..	0.0*	+0.2
30	0.80	+0.04	+0.01	-0.01	274	+49	+90	+134	1.3	0.0	+0.7	+0.1	8.6	+0.4	+7.1	+1.6
7†	0.75	+0.24	+0.21	+0.05	51	+22	+36	+26	1.2	+0.7	+1.1	+0.9	8.0	+7.2	+12.0	+10.7
WITHOUT INSULIN FOR 12 TO 20 HOURS BEFORE TEST																
1	0.80	+0.02	+0.06	-0.04	133	+63	+28	+78	1.2	0.0	+0.8	+0.3	8.6	+0.4	+9.1	+1.3
35	0.81	+0.11	+0.12	+0.05	91	+40	+66	+76	1.1	+1.6	+1.5	+0.8	8.3	+13.3	+12.7	+7.7
38	0.84	+0.06	+0.02	-0.01	104	+4	+39	+48	1.2	+0.2	+0.5	+0.4	9.2	+2.2	+5.2	+4.8
13	0.74	+0.03	+0.03	+0.03	108	+72	+100	+127	1.2	+0.4	+0.1	0.0	6.7	+5.0	+1.3	+0.3
12	0.75	+0.18	+0.21	+0.05	119	+5	+56	+55	1.3	+0.3	+0.5	+0.8	9.0	+3.8	+4.6	+9.1
INSULIN 1 TO 2 HOURS BEFORE TEST																
14	0.87	+0.10	+0.12	+0.08	53	+6	+18	+17	1.3	+0.6	+0.4	+0.2	10.0	+6.6	+6.3	+4.5
21	0.76	+0.05	+0.12	+0.04	233	+31	+2	-8	1.3	+0.6	+0.8	+0.4	7.4	+6.6	+12.2	+5.6
16	0.75	+0.09	+0.15	+0.02	140	+24	+56	-11	1.2	+0.4	+0.8	+0.6	7.0	+3.0	+9.2	+7.4
39	0.79	+0.02	-0.05	-0.04	267	-11	+56	+66	1.2	+0.3	+0.7	+0.2	8.8	+2.6	+7.1	+2.4
20 UNITS INSULIN WITH FRUCTOSE																
29	0.73	+0.16	+0.23	+0.09	76	..	+81	+35	1.2	..	+0.3	+1.3	9.0	..	+2.6	+13.1
25	0.77	+0.08	+0.13	+0.09	244	..	+26†	-57	1.2	..	+0.1	+0.8	7.9	..	+0.6	+9.8

* The changes in the blood values 1½ hours after fructose were +76, 0.0 and +0.2 mg. respectively.

† Patient had a cup of black coffee before test.

‡ The changes in the blood values 1½ hours after fructose were 0, +1 and +11.1 mg. respectively.

Fructose Without and With Simultaneous Injection of Insulin. The results of the measurements on patients to whom fructose was given orally are shown in Table 5.

Of the patients without insulin since the morning of the preceding day, 2 (Nos. 15 and 7) had marked rises in R.Q. in all periods and significant increases in PA and LA in either 2 or 3 determinations. Two patients (Nos. 36 and 30) had little or no rise in R.Q. but did have some increases in PA and LA. These 2 patients form exceptions to the general rule that the ingestion of fructose by diabetic patients is accompanied by marked rises in R.Q.

rises in PA and LA. In general, with this group there was a greater rise in PA and LA with small rises in R.Q. than occurred in similar tests with glucose.

In the group with insulin 1 to 2 hours before ingestion of the fructose, 3 patients (Nos. 14, 21 and 16) had marked rises in R.Q. in at least 2 periods, accompanied by large increases in PA and LA. One patient (No. 39) had no significant rise in R.Q. and even a fall in 2 periods, but in spite of this there were definite increases in PA and LA at all 3 periods of measurement.

The 2 patients to whom insulin was given along with the fructose had large

increases in R.Q. and increases in PA and LA, particularly at the 2 hour measurement. Patients Nos. 25 and 29 showed much greater rises in R.Q., PA and LA with fructose and insulin than with glucose and insulin and patient No. 12, to whom no insulin was given with either sugar, showed very marked rises with fructose and none with glucose. One might postulate that fructose is converted to fat more readily in the diabetic than is glucose.

Two of the patients in Table 5 (Nos. 7 and 14) who had coma within 1 week showed rises in R.Q., PA, and LA and the other one (No. 39), significant rises in PA and LA. Patient No. 21 who was insulin resistant gave large rises in R.Q. and LA and a significant rise in PA. Only 4 out of 15 patients showed no definite rise in R.Q. after fructose.

In general, with diabetic patients the ingestion of fructose is more likely to be accompanied by rises in the PA and LA of the blood, even when the rise in R.Q. is small or does not take place, and these increases are more prominent at the $\frac{1}{2}$ hour measurement than is the case after ingestion of glucose, particularly when the patients have received insulin 24 hours or less before the tests were made. Edwards and co-authors¹⁰ found that at 45 minutes after ingestion of 100 gm. of fructose normal men had increases in LA of from 7.5 to 12.7 mg. per 100 cc. of blood and that similar increases occurred at 90 minutes. The corrections in the R.Q.'s of their subjects at 45 minutes, based on changes in LA and slight changes in alveolar air, amounted to from -0.07 to -0.15 . However in the diabetics of this series, the increases in LA and PA were seldom of such magnitude. The maximum R.Q. after fructose tends to occur slightly later with diabetic patients than with normal persons. Undoubtedly some of the large increases in R.Q. with diabetic patients are due to the displacement of the carbon dioxide of the blood by the LA and PA, but in general with diabetic patients the increases in R.Q. after fructose are greater

than those after glucose. The metabolism of fructose appears to be different from that of glucose in diabetic patients as well as in normal persons.¹⁰

These studies contribute to the "under-oxidation" theory of diabetes and show that the action of insulin is to promote the formation of PA, an intermediate which leads to oxidation. The increase in oxidation is very definitely shown in the greater rises in R.Q. when insulin is given with the sugars.

Summary. The respiratory quotient (R.Q.), the blood sugar, and the pyruvate (PA) and lactate (LA) levels of the blood were determined in diabetic patients before and after the oral ingestion of 50 gm. of glucose or fructose.

In a group of 26 patients who had been without insulin for varying lengths of time preceding the tests, slight rises in R.Q. after ingestion of glucose were not generally accompanied by rises in PA and LA, but when the rise in R.Q. was 0.05 or over, there was usually a rise in either PA or LA or both. With one exception, when there was no rise in R.Q. there were no significant changes in the acid levels of the blood.

In a group of 20 patients, when insulin was given immediately preceding or immediately following the ingestion of glucose, the majority showed rises in the R.Q. and acid levels of the blood, and these changes were in some patients larger than would occur with the majority of normal subjects. Insulin resistant cases required large amounts of insulin to produce a rise in R.Q. after administration of glucose. The rises in R.Q. could have been due only partially to the displacement of carbon dioxide from the blood by the organic acids.

The ingestion of 50 gm. of fructose by 15 patients produced a rise in R.Q. in 10 of them, and in all of them the PA and LA levels were increased even when no rise in R.Q. took place. In only 2 patients was the ingestion of fructose accompanied by simultaneous injection of insulin. The

risers in R.Q. and organic acid levels of the blood were, in general, larger than after the same amount of glucose. The intermediary metabolism of fructose is, with diabetic patients as with normal subjects, different from that of glucose.

REFERENCES

1. BARKER, E. B., and SUMMERSON, W. H.: The Colorimetric Determination of Lactic Acid in Biological Material, *J. Biol. Chem.*, **138**, 535, 1941.
2. BENEDICT, F. G.: Der Helm-Respirationsapparat in seinen verschiedenen Formen, Abderhalden's Handb. d. biolog. Arbeitsmethoden, Abt. IV, T. **13**, 465, 1933.
3. BUEDING, E., STEIN, M. H., and WORTIS, H.: Blood Pyruvate Curves Following Glucose Ingestion in Normal and Thiamine-Deficient Subjects, *J. Biol. Chem.*, **140**, 697, 1941.
4. BUEDING, E., WORTIS, H., and FEIN, H. D.: Pyruvic Acid Metabolism in Diabetes Mellitus, *Am. J. Med. Sci.*, **204**, 838, 1942.
5. BUEDING, E., FAZEKAS, J. F., HERRLICH, H., and HIMWICH, H. E.: Effect of Insulin on Pyruvic Acid Formation in Depancreatized Dogs, *Science*, **95**, 282, 1942; Effect of Insulin on Pyruvic Acid Formation in Depancreatized Dogs, *J. Biol. Chem.*, **148**, 97, 1943.
6. BUEDING, E., and WORTIS, H.: The Stabilization and Determination of Pyruvic Acid in the Blood, *J. Biol. Chem.*, **133**, 585, 1940.
7. CATHCART, E. P., and MARKOWITZ, J.: The Influence of Various Sugars on the Respiratory Quotient: A Contribution to the Significance of the R.Q., *J. Physiol.*, **63**, 309, 1927.
8. CARPENTER, T. M.: Ein Apparat zur Analyse von Gasen aus Respirationskammern für Menschen und Tiere, Abderhalden's Handb. d. biolog. Arbeitsmethoden, Abt. IV, T. **13**, 593, 1933.
9. CHESLER, A., and HIMWICH, H. E.: A Comparison of the Relationship of Lactic Acid and Pyruvic Acid in the Normal and Diabetic Dog, *J. Biol. Chem.*, **155**, 413, 1944.
10. EDWARDS, H. T., BENSLEY, E. H., DILL, D. B., and CARPENTER, T. M.: Human Respiratory Quotients in Relation to Alveolar Carbon Dioxide and Blood Lactic Acid After Ingestion of Glucose, Fructose, or Galactose, *J. Nutr.*, **27**, 241, 1944.
11. FOLIN, O.: A New Blood Sugar Method, *J. Biol. Chem.*, **77**, 421, 1928; A Supplementary Note on the New Ferricyanide Method for Blood Sugar, *J. Biol. Chem.*, **81**, 231, 1929.
12. JOSLIN, E. P.: Diabetic Metabolism With High and Low Diets, Washington, Carnegie Inst. of Washington, Pub. 323, p. 77, 1923.
13. KLEIN, D.: The Effects of Administration of Glucose and Insulin on Blood Pyruvate and Lactate in Diabetes Mellitus, *J. Biol. Chem.*, **145**, 35, 1942.
14. ROOT, H. F., and CARPENTER, T. M.: The Effect of Glucose Administration in Diabetic Acidosis, *Am. J. Med. Sci.*, **206**, 234, 1943.
15. SOSKIN, S.: The Blood Sugar: Its Origin, Regulation and Utilization, *Physiol. Rev.*, **21**, 140, 1941.

HUMAN UTILIZATION OF BIOTIN FROM VARIOUS DIETS*†

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THE importance of biotin in the nutrition of man and animals has received considerable attention recently. Findlay and Stern² first suggested that a dermal and nervous syndrome of childhood called Swift's disease or pink disease showed a similarity to manifestations in rats fed a diet high in uncooked egg white. György mentioned several times the possible rôle in the prevention of human disease of the anti-egg white injury factor, called vitamin H by György.^{4,5,6} An induced deficiency of biotin was brought about by including uncooked egg white in the diet of a group of men and was cured by a biotin concentrate (Sydenstricker, *et al.*¹⁸). The relation of biotin to certain pathologic states is still unsettled. A reduction in incidence of malaria in chickens and ducks when an adequate amount of biotin was present in the diet was demonstrated by Trager.¹⁹ West and Woglom²⁰ reported that the biotin of tumor tissue was sometimes higher than that of normal tissues. Oppel¹³ found little difference in the total urinary biotin of normal individuals and those with a variety of diseases. The urinary excretion of biotin of normal persons varied from 14 to 111 μ g. per 24 hours and the daily fecal output varied from 86 to 191 μ g. Biotin output in the urine and feces was 3 to 6 times as great as the intake from the diet (35 to 60 μ g. per day), indicating synthesis of biotin, probably by intestinal microorganisms.

Little is known concerning the utilization by human beings of biotin from different sources. The balance between biotin intake and output during the consumption

of a milk diet was recently reported from this laboratory (Gardner *et al.*³). The present paper reports four balance studies comparing the utilization by college women of biotin from diets containing different amounts of baker's yeast and beef liver. The human utilization of thiamine and riboflavin on two of these four diets has been reported elsewhere (Parsons and Collord¹⁴) and the utilization of biotin of these two diets has been presented in part (Parsons *et al.*¹⁵).

Experimental. Subjects. In the 4 metabolism studies presented, uniform weighed diets were consumed by a total of 15 healthy and reliable young women, 19–25 years of age. There were 4, 6, 2 and 3 subjects on Studies 1 through 4, respectively.

Diets. A uniform diet of moderate biotin content was supplemented daily with fresh baker's yeast (3, 4 or 7½ cakes weighing approximately 12 gm. each) or beef liver (77 or 185 gm. raw). The experimental Studies 1 through 4 as given in Table 2 lasted 13 to 15, 22, 8 and 18 days.

The original basal diet was planned for the study of the human metabolism of certain B vitamins in yeast. The diets in Studies 1 and 2 (Table 1) were those described by Parsons and Collord.¹⁴ The various diets differed only in minor details according to the preference of the members of the squad. The amount of grape jelly, butter, and mayonnaise, as well as the amount and kind of bread was adjusted. Potato was substituted for squash in the studies following Study 1. The diet in Studies 3 and 4 contained less milk in order that a greater proportion of the biotin intake would be derived from bakers' yeast or beef

* Published with the approval of the Director of The Wisconsin Agricultural Experiment Station.

† This study was supported, in part, by a grant from The Nutrition Foundation, Inc.

liver. Pudding or bananas replaced ice cream for the same reason.

Since the basal diet was low in thiamine, 1 mg. per person was added daily during Study 1 and during the basal periods when no yeast or liver was consumed during Studies 2, 3 and 4.

The sequence and length of periods, the number of subjects and the supplements in the four studies are shown in Table 2.

During Studies 1 and 4, one-third of the yeast was eaten with each meal; during the second study 2 cakes were eaten with noon lunch and 1 with each of the other meals.

Methods. Twenty-four hour urinary collections were made in brown glass bottles containing 3 ml. of glacial acetic acid and 1 ml. of chloroform and were preserved with a layer of toluene. The urine was assayed for biotin after dilution. In some cases

TABLE 1.—COMPOSITION OF DIETS

		Basal diet			
		Plus raw or boiled yeast (Study 1)	Plus yeast treated 3 ways (Study 2)	Plus beef or liver (Study 3)	Plus yeast or liver (Study 4)
Breakfast:					
grapefruit juice	Gm.	200	200	150	150
bread, white	"	44	43	44	44
butter	"	10	12	10	12
grape jelly	"	30	15	10	
coffee, <i>ad lib.</i>					
Lunch:					
cheese sandwiches					
cheese, cheddar	"	55	55	50	60
bread, white	"	44	60		
bread, whole wheat	"	60	60
butter	"	10	15	20	15
lettuce	"	60	60	60	60
mayonnaise	"	..	10	15	10
apple	"	150	150	150	150
whipped cream	"	15			
sugar	"	2			
milk	"	240	240	200	200
Dinner:					
tomato juice	"	200	200		
lean beef, ground	"	150	100	180	150
cabbage	"	30	30	50	50
squash	"	100			
bread, white	"	22	22	16	16
butter	"	10	15	15	15
ice cream, vanilla	"	100	50		
ice cream, chocolate	"	..	50		
potato	"	..	100	150	125
pudding, cornstarch	"	100	
bananas	"	50	100
liver or beef	"	185*	77*
biotin content of liver	μg.	140	86
yeast, bakers', number of cakes		3†	4†	..	7.5†
biotin content of yeast	"	24	34	..	57
milk	Gm.	240			
Biotin content of basal diet	μg.	21	35	21	36

* Beef liver replaced ground beef during Period III, Study 3, and Period IV, Study 4 (Table 2).

† Baker's yeast was added to the basal diet during Periods II and IV, Study 1; Periods II, IV and VI, Study 3; and Period II, Study 4 (Table 2).

The yeast was consumed either fresh (mixed with water or fruit juice), boiled 2 minutes in water, or autolyzed 2 hours at room temperature with 2 ml. of ethyl acetate per cake of yeast. The autolysis was followed by boiling 1 hour to remove the acetate.

(Study 1) several 24 hour collections from each subject were composited to obtain a representative value for a single period.

Fecal collections were made except in Study 1. Fecal eliminations of 3 of the 6 subjects in Study 2 were collected. Charcoal and carmine were consumed on alternate

days to mark the feces. Each fecal elimination was collected directly in a 2% glacial acetic acid-alcohol mixture (Knott⁸). The samples were dried until brittle at 43° to 50° C. for 24 to 48 hours, ground and bottled. A 1 gm. aliquot was hydrolyzed with 20 ml. of 2N H₂SO₄ at 120° C. for 2 hours, neutralized with solid NaOH to about pH 3.5, filtered, and brought to a volume of 30 to 40 ml., and assayed for biotin content.

at 120° C. Six N H₂SO₄ for 4 hours at 120° C. liberated the maximum of biotin from beef liver.

Biotin was determined by a slight modification of the yeast-growth method of Snell, Eakin and Williams¹⁷ with *Saccharomyces cerevisiae* Strain 139. Test tubes 25 x 200 mm. in size were used instead of Erlenmeyer flasks. Three different amounts of the sample containing from 25 to 100 μ g. of biotin in a

TABLE 2.—URINARY AND FECAL BIOTIN DURING 4 STUDIES

Subjects, No.	Period		Diets in various studies	Biotin intake (μ g.)	Daily biotin elimination			
	No.	Days			Urine		Feces	
					Range (μ g.)	Av. (μ g.)	Range (μ g.)	Av. (μ g.)
<i>Study 1</i>								
4	I	1-2	Basal*	21	22- 46	30		
	II	3-4	Basal + 3 boiled yeast cakes*	45	21- 29	26		
	III	2	Basal*	21	21- 31	27		
	IV	2-4	Basal + 3 fresh yeast cakes*	45	21- 30	26		
<i>Study 2</i>								
6	I	3	Basal*	35	20- 36	28	57-106	82
	II	4	Basal + 4 boiled yeast cakes*	69	20- 39	30	17-114	65
	III	2	Basal*	35	21- 33	28	52- 73	61
	IV	4	Basal + 4 fresh yeast cakes*	69	16- 37	26	27-107	71
	V	2	Basal*	35	25- 37	33	39- 83	65
	VI	4	Basal + 4 autolyzed yeast cakes*	69	22- 49	35	20-109	75
	VII	3	Basal*	35	16- 39	27		
<i>Study 3</i>								
2	I	1	Unrestricted		27- 35	31	105	
	II	1st	Basal with beef*	21	24- 37	31	57-202	132
	II	2nd	Basal with beef*	21	25- 40	32	65- 72	69
	II	3rd	Basal with beef*	21	25- 37	31	53- 72	63
	II	4th	Basal with beef*	21	33	33	20-123	72
	III	1st	Basal with beef liver	161	90- 95	93	48- 51	49
	III	2nd	Basal with beef liver	161	128-146	137	48- 75	61
	III	3rd	Basal with beef liver	161	114-183	148	65- 78	71
	III	4th	Basal with beef liver	161	141-165	153	36- 62	49
	IV	1	Unrestricted		84- 91	87	90	90
<i>Study 4</i>								
3	I	3	Basal*	36	11- 34	23	41- 61	50
	II	4	Basal + 7½ boiled yeast cakes	93	20- 42	27	65-101	84
	III	3	Basal*	36	11- 29	22	66-118	91
	IV	4	Basal with beef liver	122	30- 83	60	72- 81	76
	V	4	Basal*	36	19- 59	33	55-100	72

* 1 mg. of thiamine hydrochloride added daily to basal diet.

The biotin content of the food was determined on aliquots of the foods consumed by the subjects. The weighed aliquots were homogenized in a Waring blender, hydrolyzed, neutralized and filtered in the same manner as the fecal samples.

The biotin contents of the beef liver and bakers' yeast were assayed separately from the rest of the foods. A maximum amount of biotin was liberated from the yeast by the methods tried with 4N H₂SO₄ for 4 hours

maximum of 2 ml. of solution were used. These levels of biotin are within the part of the standard curve obtained with pure biotin which forms a straight line. The addition of casein hydrolysate increases the range of biotin concentrations which can be measured by this method according to Hertz.⁷ The curves for concentrations of pure biotin by the method of Snell *et al.*¹⁷ and Hertz⁷ coincide at the levels measured in the present studies.

The turbidity produced by the yeast growth in a sample tube after incubation at 30° C. for about 16 hours was compared with that of free acid biotin in an Evelyn photoelectric colorimeter using a 540 μ filter. If the three levels of the same sample did not agree within 10% of the lowest figure, the assays were repeated.

Results and Discussion. The urinary output is generally assumed to represent an excess of a vitamin not retained by the body and is believed to be an indirect indication of the amount used for maintenance, growth or storage. Thus, when the output of biotin exceeds the dietary intake there is either synthesis (Oppel¹³), removal from body stores or a combination of these two factors. Oppel¹³ found relatively "normal" biotin excretion in fasting human subjects and those consuming egg-white for short periods. Therefore, he suggests that the level of urinary biotin is based on "biotin synthesis by colonic bacteria, and superimposed on this, sudden variations . . . due to changes in biotin content of the diet."

The urinary biotin of the 10 subjects during Studies 1 and 2 (Table 2) was not increased when the biotin intake was doubled (21 μ g. increased to 45 μ g. in Study 1, 35 μ g. to 69 μ g. in Study 2) by the inclusion daily of 3 or 4 cakes of fresh or boiled yeast. Urinary biotin during the basal periods accounted for an average of 110% of the biotin intake, while only an average of 45% of the intake appeared in the urine when fresh or boiled yeast was consumed. The absolute amounts of biotin excreted during the basal periods and the periods with fresh or boiled yeast were almost identical (average of 29 μ g. for basal periods; 28 μ g. for fresh and boiled yeast periods). These results are in contrast to the human utilization of thiamine and riboflavin in yeast in Study 1 (Parsons and Collord¹⁴). These workers found 2 to 3 times as much thiamine excreted when boiled yeast in contrast to fresh yeast was eaten. The excretion of riboflavin followed the same tendency.

When the yeast was autolyzed with

ethyl acetate (Period VI, Study 2, Table 2), the urinary biotin rose only slightly for the 6 subjects, an average of 5 μ g. daily over the basal periods which is equivalent to only 15% of the biotin in the ingested yeast. This slight rise in urinary biotin contrasted markedly with the sharp rise when beef liver was eaten (Study 4, Table 2).

Apparently at this level of biotin intake (69 μ g.) variations in urinary excretion of biotin were nearly masked by the relatively large amounts of biotin synthesized by intestinal bacteria as indicated by the total biotin eliminated during each of the four studies (Table 2). Only at quite high levels of biotin intake such as during the periods of liver feeding of Studies 3 and 4 did the variations in urinary biotin stand out clearly from the interfering synthesis. Other factors in addition to changes influencing microbiological synthesis of biotin, which might account for the lack of consistent urinary response to ingestion of yeast biotin are: lack of utilization of biotin from yeast, perhaps due to lack of solubility; a retention of biotin by the body; or a combination of the above.

The water-soluble biotin of the fresh, boiled and autolyzed yeast amounted to 10, 10 and 21%, respectively, of the total biotin in the yeast ingested and on a weight basis equaled 3, 3 and 6 μ g. per day (Study 2). If the proportion of biotin which is water-soluble is a measure of its availability to the animal, then one might expect the biotin of fresh and boiled yeast to be absorbed similarly and the ethyl acetate treated yeast to be more completely available. Some evidence of difficulty in digesting fresh yeast is indicated by the work of Montgomery *et al.*¹⁰ who observed that over one-half of viable yeast cells passed through the stomach without being destroyed when fresh yeast was ingested. Viable yeast was found in feces of human subjects consuming fresh yeast but not for those consuming boiled yeast or an ordinary diet (Parsons, Williamson and Johnson¹⁶).

The fecal biotin for all four studies is

shown in Table 2. During the periods of yeast feeding (Study 2), the fecal biotin for the last 2 days averaged slightly higher (7 μ g. higher daily) than during the corresponding days of the basal periods. Thus, the rise in fecal biotin accounted for only about 15% of the biotin intake from yeast.

An increase in fecal biotin could easily have been masked by changes in fecal synthesis, the yeast may have helped to make a medium less favorable for intestinal synthesis or the biotin contained in the yeast may have been utilized by the microorganisms in lieu of biotin synthesis by them. The possibility must be considered of a retention of biotin during the yeast periods, although there is no apparent reason for this inasmuch as the intake of biotin was rather liberal (Study 2).

It is possible that a longer period of adjustment to fresh yeast is necessary to reach an equilibrium in biotin excretion. There is some evidence to substantiate this need since the urinary biotin output during the basal period (V) following the ingestion of fresh yeast was noticeably higher than during the other two basal periods (III and VII, Study 2, Table 2). The first basal period is disregarded since this represents a transition from the unrestricted diet.

The purpose of Studies 3 and 4 was to determine whether or not urinary biotin could be elevated by the inclusion of moderate or large amounts of beef liver (77 and 185 gm.) and to compare the utilization of similar amounts of biotin from boiled bakers' yeast and beef liver (Study 4, Table 2). The biotin content of the diet was increased from 21 to 161 μ g. daily (Study 3) and from 36 to 122 μ g. (Study 4) by substituting beef liver for ground beef. The urinary biotin doubled or trebled on the first day of ingestion of liver and continued to rise for 3 or 4 days for both levels of liver feeding. A maximum of 183 μ g. of urinary biotin was reached for 1 subject (Study 3). A longer period is probably necessary to reach a plateau of biotin excretion on such high

levels of intake. This possibility was later substantiated (Gardner, *et al.*^{3a}.)

When the feeding of ground beef was resumed, the fall in urinary biotin was as rapid as was the rise during liver feeding. A comparison of the utilization of somewhat similar amounts of biotin from bakers' yeast and beef liver was made in Study 4 (Table 2). The inclusion of 7½ cakes of boiled yeast daily increased the biotin intake from 36 to 93 μ g. and 77 gm. of beef liver increased the intake from 36 to 122 μ g. daily. Despite the large amount of boiled yeast, the urinary biotin was raised only 3 to 5 μ g. daily for each of the 3 subjects (Table 2). These results corroborate those of Studies 1 and 2.

There was, however, a definite increase (average of 34 μ g. daily) in fecal biotin during the ingestion of 7½ cakes of yeast (Study 4). The high fecal biotin which continued through the 2-day basal period (III, Study 4) following the yeast feeding may also have been due to the yeast. In contrast, the fecal biotin was not significantly changed by the inclusion of liver (Study 3). During Study 4 the level of fecal biotin actually dropped from 91 to 76 μ g. (daily average) during the liver period. As in Study 3 the increased total biotin excretion during liver feeding was due to increased urinary output of biotin, while the reverse was true during yeast feeding.

The importance of fecal biotin is difficult to ascertain in the first place because it may be derived from several sources as follows: (1) unabsorbed food, (2) biotin absorbed from the gastro-intestinal tract and reexcreted, (3) biotin removed from body stores, and (4) biotin originating from microorganisms. With present methods it is not possible to assign the source of biotin which is eliminated or excreted. Secondly, the question of absorption from the large intestine of biotin or other substances synthesized by microorganisms needs reexamination since most of the intestinal flora occur below the level at which most of the absorption of nutrients other than water is believed to take place.

Najjar and coworkers^{11,12} have recently reported absorption of thiamine and riboflavin by man from the large intestine after large amounts of these vitamins were administered by a "retention" enema. On the other hand, Alexander and Landwehr¹ found no evidence of absorption of physiologic amounts of thiamine given in a similar manner. Mitchell and Isbell,⁹ however, found that in rats the biotin and pyridoxin synthesized by intestinal bacteria apparently moved freely from the bacterial cells into the surrounding medium and were, therefore, available for absorption.

The total output of biotin during Studies 2, 3 and 4 is interesting. The range of total output varied from 54 to 261 $\mu\text{g.}$ per diem which accounted for from 86 to 1073 % of the dietary biotin. Each of these values is for 1 day for a single individual. The greatest excess of biotin output over intake occurred during the periods of lowest intake, *i. e.*, during the basal periods. The average output during all of the basal periods of Studies 2, 3 and 4 was 100 $\mu\text{g.}$ daily or about 300 % of the biotin intake.

During the periods of yeast feeding the total biotin output averaged 103 $\mu\text{g.}$ daily or 137 % of the intake, during the liver feeding 163 $\mu\text{g.}$ or 115 %. Only on single days did the biotin output fall below the intake, *e. g.*, the first day of liver feeding (Study 3). Since the biotin output nearly always exceeded the intake, synthesis of biotin probably by microorganisms is in-

dicated. It would appear that less biotin was synthesized during the ingestion of bakers' yeast and beef liver as compared with the basal periods.

Summary. Four studies of the biotin metabolism of 15 college women who consumed uniform diets and these same diets supplemented with bakers' yeast or beef liver are presented. These diets contained from 21 to 161 $\mu\text{g.}$ of biotin per diem.

Doubling the biotin intake by the addition of 3 or 4 cakes of fresh or boiled yeast per diem failed to cause a consistent rise in urinary biotin and only a minor rise in fecal biotin was observed. Four cakes daily of yeast autolyzed with ethyl acetate increased the urinary output about 18 %, which is nearly equivalent to the water-soluble biotin from the treated yeast.

The daily addition of 7½ cakes of boiled yeast increased the urinary biotin somewhat (14 to 33 %) while a somewhat larger amount of biotin from beef liver doubled or trebled the urinary output on the first day of liver feeding. The rise continued for 3 to 4 days.

The range of biotin output in urine and feces per diem was as follows: urine 11 to 183 $\mu\text{g.}$, feces 17 to 208 $\mu\text{g.}$, total 54 to 261 $\mu\text{g.}$

The total output amounted to less than 1 to 11 times the intake depending to a large extent on the diet. The greatest excess of output over intake occurred on low biotin intake and the least excess occurred on a high biotin intake during liver feeding.

REFERENCES

1. ALEXANDER, B., and LANDWEHR, G.: *Science*, **101**, 229, 1945.
2. FINDLAY, G. M., and STERN, R. O.: *Arch. Dis. Child.*, **4**, 1, 1929.
3. GARDNER, J., NEAL, A. L., PETERSON, W. H., and PARSONS, H. T.: *J. Am. Diet. Assn.*, **19**, 683, 1943.
- 3a. GARDNER, J., PARSONS, H. T., and PETERSON, W. H.: *Arch. Biochem.*, (in press.)
4. GYÖRGY, P.: *Ztschr. f. artz. Fortbild.*, **28**, 377, 1931.
5. GYÖRGY, P.: *Trans. Kansas City Acad. Med.*, p. 157, 1935-37.
6. GYÖRGY, P.: *Arch. Derm. and Syph.*, **43**, 230, 1941.
7. HERTZ, R.: *Proc. Soc. Exp. Biol. and Med.*, **52**, 15, 1943.
8. KNOTT, E. M.: *J. Nutr.*, **12**, 597, 1936.
9. MITCHELL, H. K., and ISBELL, E. R.: *Univ. Texas Pub.*, No. 4237, p. 125, 1942.
10. MONTGOMERY, B. E., BOOR, A. K., ARNOLD, L., and BERGHEIM, O.: *Proc. Soc. Exp. Biol. and Med.*, **28**, 385, 1931.
11. NAJJAR, V. A., and HOLT, L. E.: *J. Am. Med. Assn.*, **123**, 683, 1943.
12. NAJJAR, V. A., JOHNS, G. A., MEDIAIRY, G. C., FLUSHMANN, G., and HOLT, L. E.: *J. Am. Med. Assn.*, **126**, 357, 1944.

13. OPPEL, T. W.: J. AM. MED. SCI., 204, 856, 1942.
14. PARSONS, H. T., and COLLOD, J.: J. Am. Diet. Assn., 18, 805, 1942.
15. PARSONS, H. T., COLLOD, J., GARDNER, J., STRONG, F. M., and PETERSON, W. H.: Fed. Am. Soc. Exp. Biol., Fed. Proc., 1, 129, 1942.
16. PARSONS, H. T., WILLIAMSON, A., and JOHNSON, M. L.: J. Nutr., 29, 373, 1945.
17. SNELL, E. E., EAKIN, R. E., and WILLIAMS, R. J.: J. Am. Chem. Soc., 62, 175, 1940.
18. SYDENSTRICKER, V. P., SINGAL, S. A., BRIGGS, A. P., DEVAUGHN, N. M., and ISBELL, H.: Science, 95, 176, 1942; J. Am. Med. Assn., 188, 1199, 1942.
19. TRAGER, W.: Science, 97, 206, 1943.
20. WEST, P. M., and WOGLOM, W. H.: Science, 93, 525, 1941.

CHLOROMA—A CLINICO-PATHOLOGIC STUDY OF TWO CASES

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CHLOROMA is a rare disease. The 2 instances reported in this paper are the only ones so diagnosed at Duke Hospital among 226,796 patients. In both instances tumors were the presenting signs, and the clinical course was rapidly downhill.

No attempt was made to review the literature. An excellent bibliography and résumé of the subject may be obtained from Forkner's book on "Leukemia and Allied Disorders."

Case Reports. CASE 1. (Unit B-23978).

Clinical History. A 7 year old colored boy was admitted to the Eye Service on Feb. 29, 1944, with a marked exophthalmos on the left. (Fig. 1.) A letter from the referring physician stated that the patient had had a throat and ear infection 2 mos. previously, and at that time developed a facial paralysis with edema of both eyes. One week before admission there was a recurrence of orbital edema, bilaterally, but more marked on the left. The patient was sent with a tentative diagnosis of retro-orbital tumor or cavernous sinus thrombosis.

Physical Examination. Temperature, 38.8°; pulse, 120; respirations, 22. The patient was a poorly nourished Negro boy, who was acutely ill and complaining of pain in the abdomen and left eye. There was a marked bony swelling over the left zygoma which was non-tender. The left eye almost protruded from the orbit, with marked chemosis and excoriations of the conjunctiva and edema of the orbit. (Fig. 1.) Some exophthalmos was present on the right, but no chemosis. There was a bilateral diminution of hearing. The abdomen was moderately distended and tympanitic. The liver border was barely felt. Remainder of physical examination was non-contributory.

Accessory Clinical Findings. Hemoglobin, 7.3 gm. (47%); erythrocyte count, 2,330,000; leukocyte count, 232,000, with the following

differential formula: myeloblasts, 85%; undifferentiated myelocytes, 10%; neutrophilic myelocytes, 4%; and eosinophilic myelocytes, 1%. (Fig. 2.) Examination of the smear showed moderate anisocytosis and poikilocytosis. No nucleated red cells were seen. Platelets were 100,000 per c.mm. and reticulocytes estimated at 1%. Sternal puncture showed the leukocytes to number 480,000 per c.mm. There was a scarcity of nucleated red cells. Reticulocytes were estimated at 2%. There was a marked hyperplasia of the embryonic cells, similar to those seen in the peripheral blood. These cells were definitely myeloid. On dark-field examination the characteristic refractile granulation was present in the majority. Goodpasture stain gave a positive peroxidase reaction. In some, the nucleus was distorted, probably indicating mitosis. Differential on bone marrow: myeloblasts, 82%; undifferentiated myelocytes, 10%; neutrophilic myelocytes, 7%; eosinophilic myelocytes 1%. An average of 1 erythroblast was seen for every 100 white blood cells. Blood Kahn, Kline, and Mazzini were negative. Roentgen rays of the sinuses showed a large soft tissue shadow overlying the left orbit. The right antrum and ethmoids on both sides appeared to be cloudy. Mastoid cells showed a somewhat hazy outline along the septa. A Roentgen ray of the chest showed a haze over the entire right chest, due to pleural reaction, and a fuzzy increase in lung markings in the right base and left upper lobe. No definite glandular enlargement was seen. Urine examination revealed a specific gravity of 1.104; reaction, acid; sugar, none; albumin, 3+. Microscopic examination of the sediment showed 3 to 4 white blood cells per high-power field and an occasional granular cast. Acetone reaction was 2+, and the test for diacetic acid was positive.

Course in Hospital. The patient was put at bed rest and sedated with codeine and

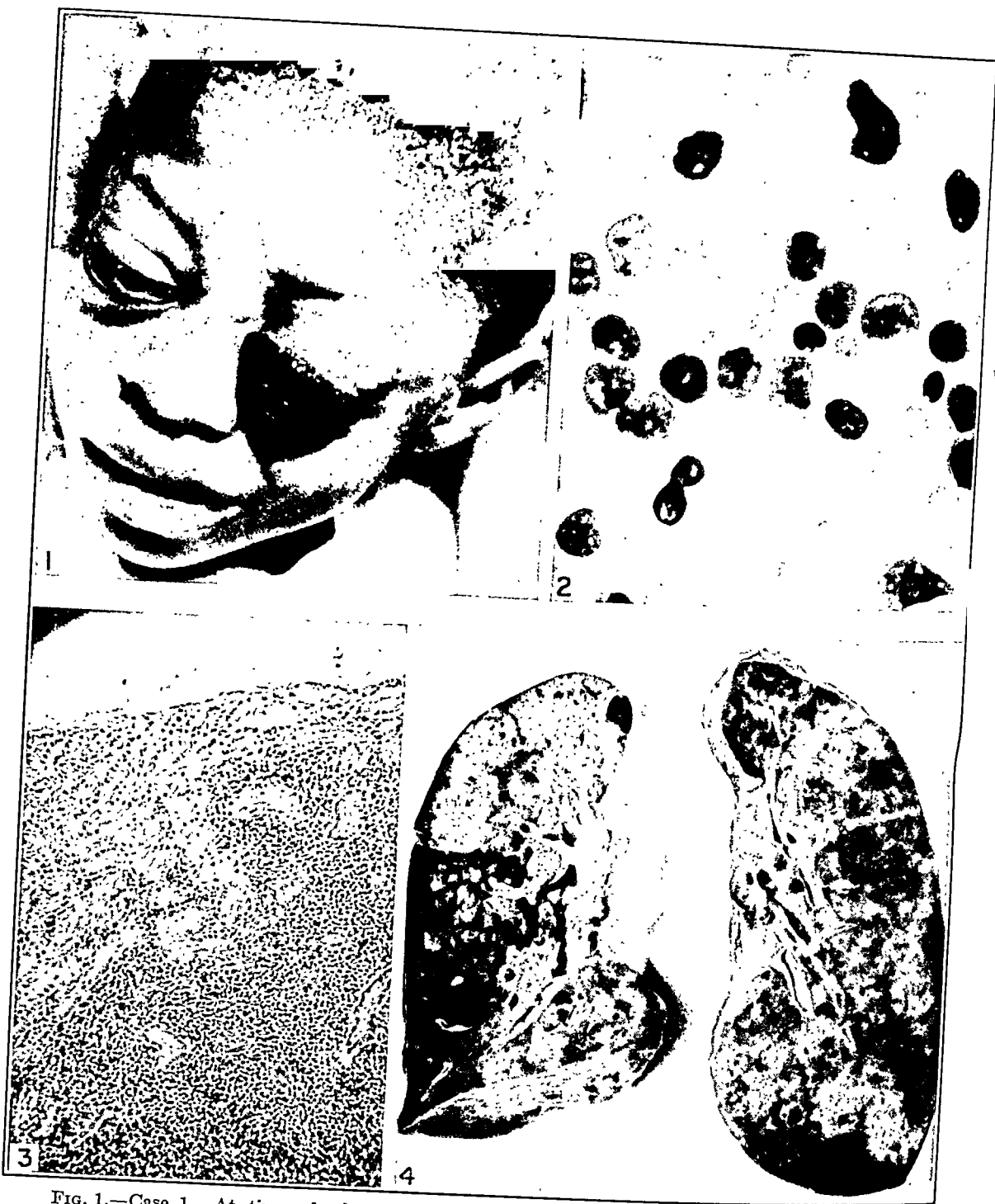


FIG. 1.—Case 1. At time of admission, showing extreme proptosis of left eye and beginning exophthalmos on right.

FIG. 2.—Case 1. Smear of peripheral blood, showing predominance of myeloblasts.

FIG. 3.—Case 1. Microscopic section of kidney showing compression and infiltration of kidney parenchyma by chloroma nodule.

FIG. 4.—Case 1. Lungs showing enlarged hilar nodes and massive consolidation.

aspirin whenever necessary for relief of pain. The left eye was protected by saline compresses. Four 250-cc. transfusions of whole blood were given and also several injections of intravenous dextrose. His temperature ranged between 38° and 40° C. for the first 4 days in the hospital. He was then started on 10 cc. of methylene blue (10 mg. per cc.) intravenously each day for 4 days. The temperature dropped below 38° C. while on this medication, but his pulse rate remained around 120. Because of the hopeless outlook and scarcity of veins, methylene blue was discontinued, following which his temperature again rose to the former level between 38° and 40° C. A clinical analysis of the urine revealed large amounts of porphyrin, but this was after the patient had received 2 blood transfusions. The patient became progressively worse and expired on the 15th hospital day.

Autopsy Findings. (No. 4022.) Acute myeloblastic leukemia; porphyrinuria; chloroma of right auricular appendage, kidneys, bladder, bile ducts, skull, scalp; (history of blindness), chloroma of right and left orbits with extreme proptosis, chemosis, keratitis, iritis; hepatomegaly, splenomegaly, general glandular enlargement; diffuse myeloid alteration of bone marrow, lymph nodes, liver, spleen, pleura, lungs, pericardium, diaphragm, choroid and sclera; petechial hemorrhage in epicardium, pleura, renal pelvis, testis and retina; bilateral confluent lobular pneumonia, fibrinopurulent pleurisy, serosanguineous pleural effusion.

Gross Examination. Autopsy was performed 6 hours after death. The enlargement of the cervical, axillary and inguinal nodes was accentuated by the juvenile thin, bony body. Twelve small, firm, pea-sized, movable nodules were palpated in the scalp. The eyelids were stretched to 3 times normal size because of the extreme proptosis. Bloody, frothy fluid poured from the nose.

The centers of the enlarged mediastinal lymph nodes like those of the rest of the body were gray-green, exhibiting an infiltrating type of reaction, rather than the homogeneous alteration characteristic of lymphoid leukemias. No remnant of thymus could be identified in the small green mass of matted nodes attached to the upper anterior pericardium.

The right and left pleural cavities each contained 400 cc. of serosanguineous fluid.

Shaggy fibrinopurulent adhesions covered the pleural surfaces of the lungs, which were completely solidified by hemorrhage, edema and confluent areas of pneumonic consolidation. (Fig. 4.)

Numerous petechiae dotted the epicardium. A glistening lime-green nodule 0.7 cm. in diameter was found on the right auricular appendage, and a similar flattened mass was seen beneath the endocardium of the left ventricle.

The liver was twice its normal size. The endothelial lining of the larger vessels was a distinct light green. Two soft, rather friable, unencapsulated, olive-green masses, 3 x 2 x 0.5 cm., were located along the course of the common bile duct, surrounding but not obstructing it. The spleen was moderately enlarged, and its firm red pulp bulged from the tight capsule. The adrenals were normal.

Both kidneys were greatly enlarged. The cortex of each exhibited 4 or 5 small raised nodules with hemorrhagic borders and green centers. Several similar masses noted in the bladder wall were also characterized by the unique yellow-green color seen in varying concentrations in the urine, endothelium, connective tissue, and periosteum. (Fig. 6.)

Additional green nodules were seen in the scalp, calvarium, and dura. No lesions of the brain or cranial nerves were demonstrated.

Attached to the periosteum of the posterior portion of each orbit was a soft flattened dirty green mass which extended inferiorly to the sheath of the optic nerve and laterally to the lacrimal glands. Dense infiltration of the orbital fat, choroid, and sclera were noted, in addition to the small retinal hemorrhages. There was edema, inflammation, and necrosis of the conjunctiva, cornea, and iris. (Fig. 5.)

At the time of autopsy hydrogen peroxide restored the green color to the faded fresh tissue. This was not observed later on the formalin-fixed tumors. Four months after autopsy, portions of the formalin-fixed tissue were treated with glacial acetic acid and ether, and the extract examined spectroscopically for protoporphyrin, with negative results.

Bacteriology. Beta hemolytic streptococci were grown from the spleen and both lungs.

Microscopic Examination. The sections were stained with hematoxylin and eosin, Wright's stain, and Giemsa. Each oil im-

mersion field of the chloroma masses contained several eosinophils, 1 or 2 segmented neutrophils, and a few juvenile and stab forms. With the help of peroxidase and oxidase stains, most of the cells were identified as myelocytes and myeloblasts. Neutral red and brilliant cresyl blue preparations were not contributory. Scharlach Red sections on formalin-fixed tissue showed tiny round droplets of fat in the periphery of cells resembling myelocytes and metamyelocytes. The polarized light microscope failed to show any doubly refractile crystals in the chloroma mass from the left kidney.

Remnants of lymphoid follicles were noted in the "chloromas" adjacent to the bile ducts. Special stains revealed a fine reticulum of that density seen ordinarily in lymph nodes. Small blood-vessels with a fine fibrous support were moderately prominent. The tumors were not encapsulated, and the gross appearance of circumscribed nodules was found to be due to an abrupt change in the concentration of cells in the tissue. This was especially striking in the kidneys where the distribution of cells strongly resembled metastatic lymphosarcoma. (Fig. 3.)

The liver, spleen and lymph nodes ex-



FIG. 5.—Case 1. Low-power view of orbital tissue. Note large chloroma in superior and posterior orbit and sprinkling of cells about optic nerve, muscles, and retina.

FIG. 6.—Case 1. Urinary tract showing many nodules in both kidneys and in bladder. Note hemorrhagic borders of chloroma.

hibited the diffuse infiltration typical of myeloid leukemias, whereas the bone marrow was filled with proliferating cells. Many gram-positive cocci were stained in the consolidated portions of the lungs. These were accompanied by a massive infiltration of early myeloid cells.

CASE 2. (Unit B-26796). *Clinical History.* A 33 year old married male was admitted on April 14, 1944, because of a suspected brain tumor. He dated the onset of his illness 6 weeks previously, when he struck his head on a weight, after which a small nodule appeared on the occipital area of his head. The nodule grew rapidly and was excised. On study of sections of this tissue, the pathologist was unable to make a definite diagnosis. Three weeks following the initial episode, he developed severe occipital headaches radiating down the left side of his neck. He was admitted to another hospital, and while there developed diplopia and left-sided weakness. During the hospitalization, 2 lumbar punctures were done, and the spinal fluid found to be under increased pressure. He was referred with a tentative diagnosis of brain tumor.

Physical Examination. Temperature, 37.8°; pulse, 99; respirations, 18; blood pressure, 130/75. The patient was a well-developed and well-nourished young man who was acutely ill and quite uncomfortable. All of the superficial lymph nodes were palpable, firm, shotty, movable, and non-tender. The face was asymmetrical due to a left facial palsy, and there was some proptosis of the left eye. (Fig. 7.)

Numerous petechiae were scattered over the abdomen and back. There was tenderness on palpation over the left parieto-occipital area. The right pupil was much larger than the left and reacted well to light and on accommodation. The left pupil was miotic, failed to react to light, and appeared to be irregular. Extraocular movements were poorly performed due to failure of the left lid to move well and to a sixth nerve weakness. There was a bilateral diminution of hearing. There was slight pain on flexion of the neck. The chest was symmetrical and expansion was equal; however, there was a small tender nodule felt over the xyphoid process. Respirations were mainly abdominal. The lung fields were clear. No cardiac abnormalities were noted. The abdomen was flat without tenderness or

spasm. The liver border was palpable a few finger-breadths below the costal margin. The tip of the spleen was barely felt. A detailed neurologic examination revealed the following pertinent findings: (1) Bilateral papilledema with multiple exudates, hemorrhages, and scars located around the nerve heads; the retinal veins were engorged and tortuous; (2) the pupils were unequal, the right being much larger than the left; the extraocular movements were poorly performed due to sixth nerve weakness on the left; (3) there was hypalgesia over the left face, and the corneal reflex was absent on the left; (4) there was a left lower facial weakness; (5) hearing was bilaterally diminished and audiograms revealed a nerve deafness bilaterally; (6) the motor and sensory systems were intact elsewhere; reflexes were equal and active, and Babinski was negative.

Accessory Clinical Findings. Hemoglobin, 12.1 gm. (78%); erythrocyte count, 3,940,000; leukocyte count, 29,000. The differential formula revealed the following: segmented neutrophils, 5%; myeloblasts, 77%; undifferentiated myelocytes, 9%; neutrophilic myelocytes, 1%; micromyeloblasts, 1%; small lymphocytes, 5%; large lymphocytes, 1%; plasma cells, 1%. (Fig. 8.) The erythrocytes showed only slight variation in size and shape. No nucleated red cells were seen in the peripheral blood. Reticulocytes were estimated at 2%. Platelets were reduced to 100,000 per c.mm. Bone marrow studies showed a leukocyte count of 80,500 per c.mm. There were numerous myeloblasts and an occasional nucleated red cell. Differential formula: segmented neutrophils, 2%; myeloblasts, 55%; micromyeloblasts, 29%; differentiated myelocytes, 8%; eosinophilic myelocytes, 1%; small lymphocytes, 4%; large lymphocytes, 1%. An average of 1 erythroblast per 100 white blood cells could be counted. It was the impression of the hematologic consultant that this was an instance of myeloblastic leukemia and that the central nervous system findings could be explained on the basis of chloroma.

Blood Kahn, Kline, and Mazzini were negative. Blood NPN was 29 mg. %; serum calcium, 9.1 mg. %; phosphorus, 4.3 mg. %; serum protein, 6.6 mg. %. Roentgen ray of the chest showed a diffuse increase in the lung markings with an area of increased density in the right upper lung field. Roent-

gen rays of the abdomen, spine, and pelvis showed nothing abnormal; no abnormal calcifications were seen in Roentgen ray of the skull. An electroencephalogram showed slight irregularities over the right occipital area, but otherwise the record was within normal limits. Visual fields were normal. Routine urine examination was negative. Urinary porphyrins were not increased. A lumbar puncture revealed tremendously increased pressure, measured at 430 mm. of spinal fluid. There were 33 leukocytes and 10 red blood cells per c.mm. of spinal fluid. Pandy reaction was slightly positive, and

spinal fluid proteins measured 43 mg. %. The Wassermann and colloidal mastic test on the spinal fluid were negative.

Course in the Hospital. After 8 days of supportive therapy and multiple small transfusions, the patient failed rapidly. His abdomen became distended, and he was unable to swallow. There was marked urinary retention, which continued until death. New hemorrhages appeared in the left eye, and the papilledema became worse. Exophthalmos on the left became more prominent. Cheyne-Stokes respiration developed several days before death. On the day before death,

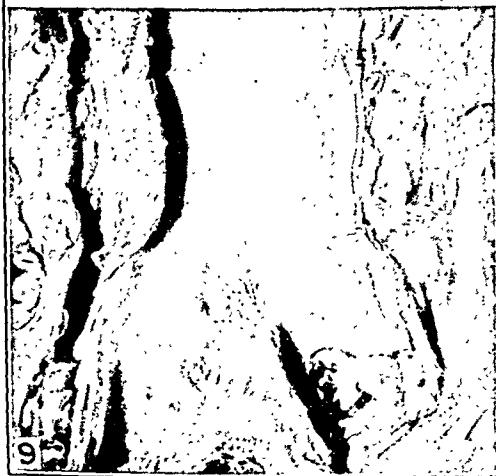
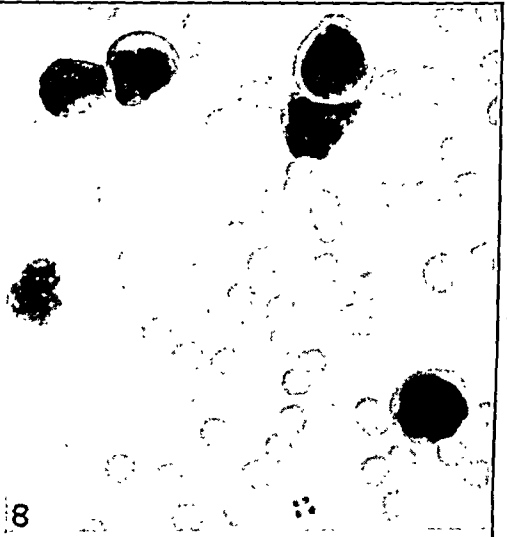


FIG. 7.—Case 2. Photograph on admission showing beginning exophthalmos of left eye.

FIG. 8.—Case 2. Smear of peripheral blood showing myeloblasts.

FIG. 9.—Case 2. Small nodule at bifurcation of trachea.

FIG. 10.—Case 2. Section of liver showing soft, well-circumscribed nodule hanging from wall of portal vein.

the left eyeball was practically protruding from the orbit, and the right eye exhibited papilledema, hemorrhage, and exudate, and bleeding continued into the skin, mucous membranes, and eyegrounds. By this time the hemoglobin had dropped to 7.8 gm. (50%), in spite of frequent transfusions; the red cell count was 2,280,000. The white count of 25,480 and the differential formula were essentially as on admission. The patient died on the 16th hospital day.

Autopsy Findings. (No. 4071.) Acute myeloblastic leukemia; chloroma of dura, trachea, mediastinum, liver, kidneys; periosteal and perichondrial chloroma of ribs, sternum, thoracic and sacral vertebrae; chloroma of left orbit, exophthalmos, chemosis, keratitis, and iritis; hepatomegaly, splenomegaly, moderate general glandular enlargement; diffuse myeloid alteration of pleura, meninges, spleen, lymph nodes, liver, and bone marrow; petechial hemorrhages of skin, gums, stomach, intestines, bladder, prostate and testis, subdural hemorrhage, cystitis, cardiac dilatation; congestion of lungs, liver, and spleen.

Gross Examination. Autopsy was performed 11 hrs. after death. The body was covered with bruises and numerous petechiae. There was a faint yellow tinge to the inelastic skin and to the sclera of the right eye, which protruded slightly. The left eye exhibited marked chemosis because of the prominent exophthalmos.

The external and internal surfaces of the ribs, manubrium, and sternum were almost completely covered by varying concentrations of soft, grayish green tissue which also transformed the vertebral column into a smooth, shiny green ridge. (Fig. 11.) In the thoracic cavity a solid rope of green tissue, 8 x 2 x 2 cm., separated the esophagus and aorta; and in the pelvis the rectum was matted to the sacral vertebrae by a similar mass.

Although there was slight general lymphoid hyperplasia, only the mediastinal and cervical lymph nodes were moderately enlarged, containing yellow-gray centers suggestive of leukemoid infiltration. A remnant of thymus was embedded in a mealy grayish green mass, 3 x 2 cm., matting together the anterior pericardium and adjacent mediastinal fascia. A soft green nodule, 1.7 cm. in diameter, projected into the lumen of the trachea. (Fig. 9.) The posterior pleural

surfaces of the edematous and congested lungs were infiltrated locally by extensions from the adjacent costal masses. (Fig. 12.) At the porta of the enlarged liver was a chloromatous nodule projecting through the wall of a vein into its lumen, and smaller localized masses marked several of the portal areas. (Fig. 10.)

The adrenals were normal. Each kidney weighed 200 gm. and showed minute hemorrhagic cortical nodules, pelvic hemorrhages and extreme thickening of the upper calyces by infiltration of grayish green tissue, the faded color of which was restored slightly with hydrogen peroxide. This phenomenon was not duplicated with formalin-fixed tissue 2 mos. later.

Examination of the skull revealed no nodules at any of the foramina. However, the meninges of the medulla, pons, base of brain, and sella turcica were slightly thickened. Several circumscribed pea-sized masses were seen on both surfaces of the dura. Beneath the dura on the left these nodules were covered by a thin coat of fresh and clotted blood extending over the entire left parietal lobe.

In the posterior portion of the left orbit was a flat disk of dirty green tissue, 4 x 2 x 1 cm. Spectroscopic examination of the formalin-fixed tissue 2 mos. after autopsy was negative.

Microscopic Examination. Sections of the rib, sternum, vertebra and femur showed the marrow to be entirely replaced by cells of the myeloid series, 80% of which were similar to those in the green tumors identified as myeloblasts by peroxidase stains. The blood-vessels showed qualitative, rather than quantitative, change in the character of the circulating leukocytes. Likewise, the sinusoids of the liver were not greatly infiltrated, except at the sites of the nodular accumulations of myeloid cells seen grossly. The pleura, lungs, renal cortices, lymph nodes and spleen showed slight but definite myeloid alteration.

The solid tumors were held together by a light fibrous stroma. No lymphoid tissue was demonstrated in the masses adjacent to the aorta, rectum, and periosteum. Special stains of these showed a light, fine reticulum. Scharlach R preparations of the formalin-fixed tissue revealed small fat droplets in the cytoplasm of some of the earlier myeloid

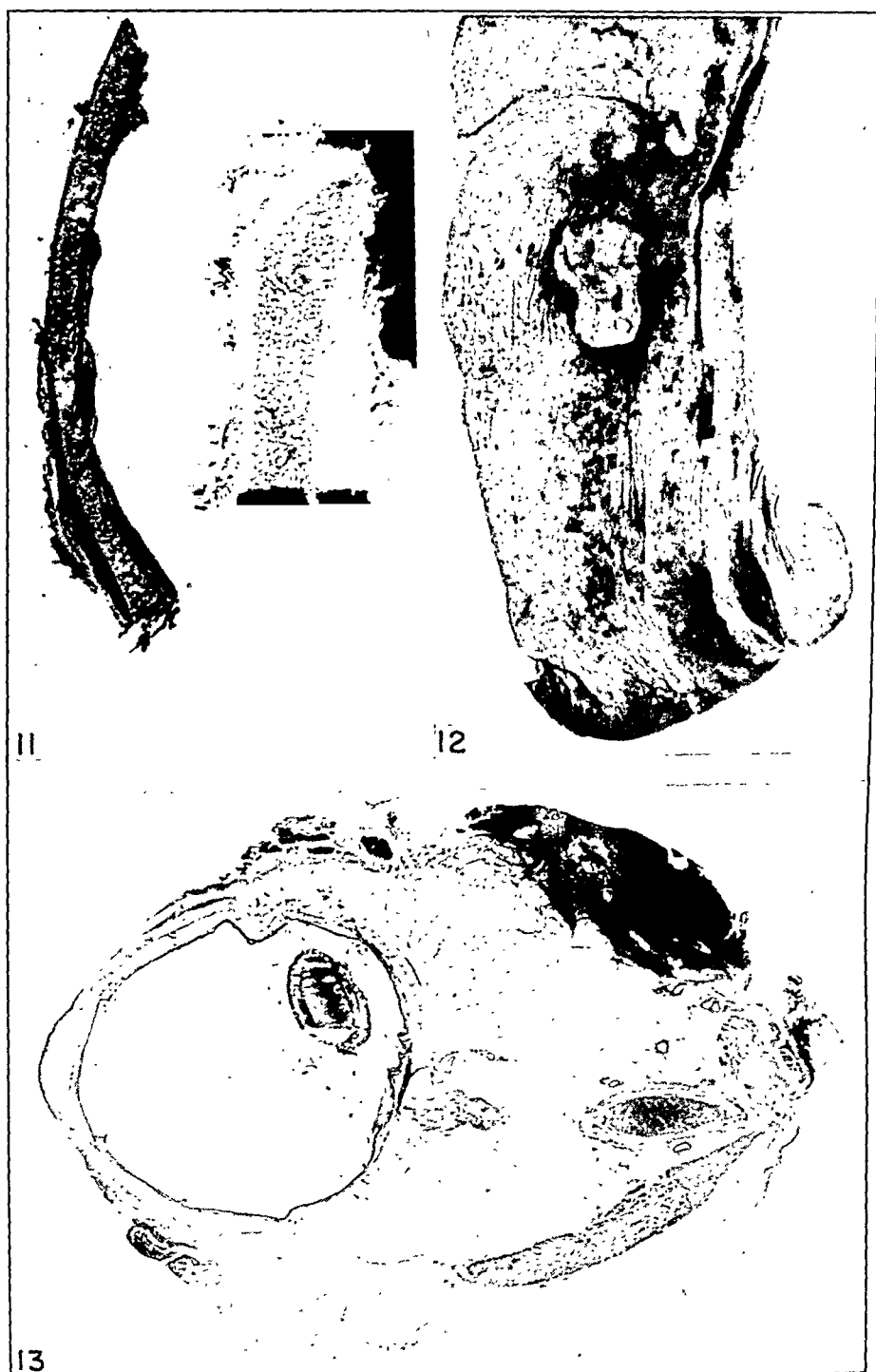


FIG. 11.—Case 2. Rib and sternum showing relation of tumor to periosteum.

FIG. 12.—Case 2. Posterior surface of left lung and masses of chloroma tissue which had extended from the adjacent rib.

FIG. 13.—Case 2. Lantern slide of eye and relation of chloroma to orbital tissue.

cells. Polarized light studies revealed no doubly refractile crystals.

The meninges over the medulla and pons were thick with myeloid cells, and occasional perivascular foci within the pons and cranial nerves were seen. Sections of the left eye showed the tips of the lacrimal glands to be embedded in the large chloroma, which also involved the periosteum of the orbit, Tenon's capsule, and the sheath of the optic nerve. The cells separated the muscle fibers and loosely infiltrated the orbital fat, posterior retina, sclera, and choroid. The iris and cornea, altered by inflammation, edema, and necrosis, exhibited no leukemic infiltration. (Fig. 13.)

Discussion. The 2 patients described showed the following clinical characteristics:

1. The presenting symptoms and signs of a rapidly growing tumor in both cases producing extreme exophthalmos.

2. The hematologic picture of an acute myelogenous (myeloblastic) leukemia.

3. A rapidly downhill course.

In Case 2 the neurologic picture was one of an infiltrating lesion in the pons, but autopsy showed only meningeal infiltration in addition to the other findings described above. In both instances the correct diagnosis was made before death.

The exact nature of the pigment which causes these peculiar "green tumors" is unknown. It is thought to be chemically related to the porphyrins. Because of this, urinary porphyrin determinations were made. The first case showed large amounts of porphyrin in the urine, the significance of which is questionable because of the transfusions given previously. In the second case porphyrin determinations were made before transfusing the patient, and there was no appreciable increase in urinary porphyrins.

At autopsy further attempts were made to study the pigment. Hydrogen peroxide characteristically restored the pigment in the fresh tissue. Polarized light studies and spectroscopic analysis were performed on formalin-fixed tissue with no contributory results. Scharlach Red stains, how-

ever, revealed a few minute fatty droplets in the cytoplasm of cells resembling earlier myeloid cells.

At autopsy the pigment was not only confined to the tumor masses, but was distributed homogeneously throughout connective tissue, mucosal surfaces, and endothelial lining. This interesting and unusual distribution is reminiscent of that of the bile pigments in cases of jaundice, and confirms previous observations that the pigment is located in the plasma of the circulating blood. We believe that it represents there an intermediary product, protoporphyrin, in the breakdown of hemoglobin to bilirubin. This is further substantiated by the fact that, although the duration of both of our cases was equal, the concentration of green pigment was greater in Case 1, in which the hemoglobin was 7.3 gm., compared to 12.1 gm. in Case 2.

The observations of these cases are in accord with those reported in the literature. The great variation in gross morphology and distribution should be emphasized.

Cases have been reported earlier in which chloromatous masses have been associated with lymphatic leukemia, monocytic leukemia, and lymphosarcoma. The hematologic methods in these cases, however, are not reliable and do not compare with techniques used today for identification of myeloblasts. It is our impression, therefore, that chloroma represents an atypical form of myeloblastic leukemia, and in distribution of cells is related to myelogenous leukemia as lymphosarcoma is related to lymphatic leukemia.

Summary. 1. The clinical and pathologic findings of 2 cases of chloroma have been presented, with results of special studies as to the nature of the green pigment characteristic of these tumors.

2. Chloroma represents a rare form of myeloblastic leukemia in which the cells show an unusual tendency toward tumor formation.

3. The pathologic findings herewith photographed and described indicate that

chloromas may be present as small, well-circumscribed nodules or as large, solid masses with particular predilection for meninges, periosteum, mucous membranes, endothelium, and mesothelium.

4. Although the exact chemical nature of the green pigment has not been demonstrated by our spectroscopic and polar-

iscopic studies, the distribution in the above cases suggests an intermediary product in the breakdown of hemoglobin to bilirubin.

5. "Chloroma" should be suspected clinically when tumors occur coincidentally with a myeloblastic leukemia.

THE NATURAL COURSE OF CHRONIC SOUTHWEST PACIFIC MALARIA

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DEFINITE knowledge concerning the natural course of chronic Southwest Pacific vivax malaria is lacking. Such a knowledge is of unusual importance at present, not only because of the large number of cases that are being observed, and because their management is unsatisfactory, but also because the effects of various forms of treatment cannot be evaluated until they are compared with the natural course of the disease when it is untreated. The generally accepted concept of the clinical course of vivax malaria is that it is a febrile disease manifested by periodic bouts of activity which are characterized by chills, fever and sweating. The periodicity is classically shown by the fever appearing on alternate days with free intervals in between, producing the well-known temperature pattern of tertian malaria. It is widely recognized that the original attack may be of short or long duration, and that there is a marked tendency for the infection to become chronic and manifest itself by relapses which resemble the original attack. However, there is no accurate information at present on whether or not the natural course of malaria in the Southwest Pacific area corresponds to the generally accepted concept of the disease which has been based on observations of malaria made in other parts of the world.

Known Effect of Anti-malaria Therapy. Although the suppressive therapy of malaria by atabrine has been proven quite satisfactory since sufficient atabrine has been administered to produce blood levels which are incompatible with parasitemia, it is recognized that suppression of clinical malaria by atabrine is of temporary value and only effective as long as the atabrine

treatment is continued. It is also known that treatment of each acute attack of malaria by a week's course of atabrine therapy is only satisfactory in aborting the attack, and does not prevent relapses from recurring. Publications are still appearing discussing the curative treatment of malaria,³ but there is no known curative treatment. Quinine is no more effective than atabrine, but it has been used very little recently because of the shortage of supply. Other forms of treatment have not proven equal to atabrine and quinine in effectiveness.

The question of the development of immunity to malaria is an important one. Immunity does develop and is parasite-strain specific, but its acquisition takes a long period of time which varies greatly in individual cases. It is known that prolonged clinical activity occurring in a patient with therapeutically induced malaria may cause the rapid development of immunity to native American strains, and the patient may become cured in the full sense of the word providing no drug treatment is given.¹ It has been suggested that Southwest Pacific malaria may also develop immunity resulting in cure if treatment is withheld.

The Natural Course of Relapsing Malaria. In a study recently carried out at Hammond General Hospital, it was planned to observe the natural course of relapsing Southwest Pacific malaria without treatment in order to ascertain whether or not immunity might develop with sufficient rapidity to warrant the clinical use of so-called "non-specific therapy" (no treatment) in the management of the malaria problem in soldiers returning from the Pacific area. While carrying

out this program, specific treatment was withheld as long as the patient's clinical condition was satisfactory; but in every instance the patient had received suppressive treatment overseas or treatment of the original attack overseas so that his clinical malaria was only untreated in the later stages, and its complete natural course may have been altered by therapy carried out before coming under our observation. However, we were able to study 72 patients who volunteered to take part in the program, and in 23 of them no specific treatment of any sort was ever carried out at Hammond General Hospital. In 19 others specific treatment was utilized for administrative reasons only at some one time during the observations made, and 17 cases had to have drug therapy for all clinical activity because of the severity of their infection. Two patients had parasitemia only.

Although we have made no initial observations from which to illustrate the early course of the disease, a number of reports indicate that at onset fever occurs irregularly and does not follow the common tertian pattern. The duration of fever is also variable and there is nothing about the temperature chart to suggest vivax malaria as it is usually described in standard texts.² We have, however, been able to identify the manifestations of the onset of this disease in other patients who were under suppressive atabrine therapy in the Southwest Pacific area, and, subsequently developed their first clinical attacks of malaria in the United States. This initial period of onset of the disease has been designated as Phase 1, and probably the majority of patients in this phase have no recurrences following one or two attacks. However, once the disease becomes chronically relapsing, it assumes a somewhat different course.

Present Study. The patients under observation started on the program having previously had from 1 to 16 relapses. The average number of previous attacks per patient was 6.64 for 69 patients. As a rule, each acute relapse had been

treated previously. We have designated this chronic relapsing stage, in which frequent recurrences have become well established, as Phase 2 or the intermediate phase of the disease (Chart 1). When drug therapy is withheld, the natural course of Phase 2 is typified by relapses, each of which may include recurrent "bouts" of chills and fever. These "bouts" of clinical activity tend to assume the single tertian pattern, but may assume a double tertian pattern. Each relapse may last from 1 day to more than 3 months. The average duration of 113 untreated attacks was 5.47 days. Between these "bouts" of fever (fever is taken to be a temperature of 100° F. by mouth or over) there is usually clinical activity in that the patients do not feel well and there may be headache, some generalized aching and slight rises in temperature. The blood studies usually reveal the presence of parasites during the active periods of this phase. Clinical activity may subside after a single "bout" of fever, or may recur for months.

Following this second phase which is punctuated by irregularly occurring "bouts" of clinical activity with parasitemia, a third phase of the disease occurs which may be terminal. During this final phase there are few or no clinical symptoms, and the temperature does not rise above 100°, but parasitemia is constantly or irregularly present. Phase 3 lasted from 10 to 80 days in 30 cases which were completely followed, and apparently represents the development of immunity and perhaps cure (Chart 2). However, even after a patient has passed through all three phases of the disease, an occasional late relapse might occur. No such relapse was noted in our series during the period of follow-up observation which was continued for at least 3 months in each case of the entire series.

Results of the Special Program Study. The patients on this non-specific malaria therapy program were under observation for from 2 to 10 months. The natural course of the disease during the second

and third phases seems to have been sufficiently well studied to draw the conclusion that Phase 2 ordinarily takes many months, and that Phase 3 may last many weeks. This makes the therapeutic procedure of inducing immunity by withholding drug therapy an impractical procedure in military medicine. However, the observations carried out make possible a clearer conception of the disease and certainly afford a better basis for judging the effects of treatment than has heretofore been possible. This is well illustrated by the fact that the cyclic

recurrences which have been considered so characteristic of Southwest Pacific malaria very rarely occurred when treatment was withheld. In 1943 in calculating the incidence of relapses in a series of 169 atabrine treated cases, we found that there were 424 attacks in the group, when relapses were analyzed in patients having up to 11 attacks. In the majority of these patients, the period between attacks was so constant that the time of the next attack could be predicted with surprising accuracy. The average time of the recurrence was every 34 days, with 97.8%

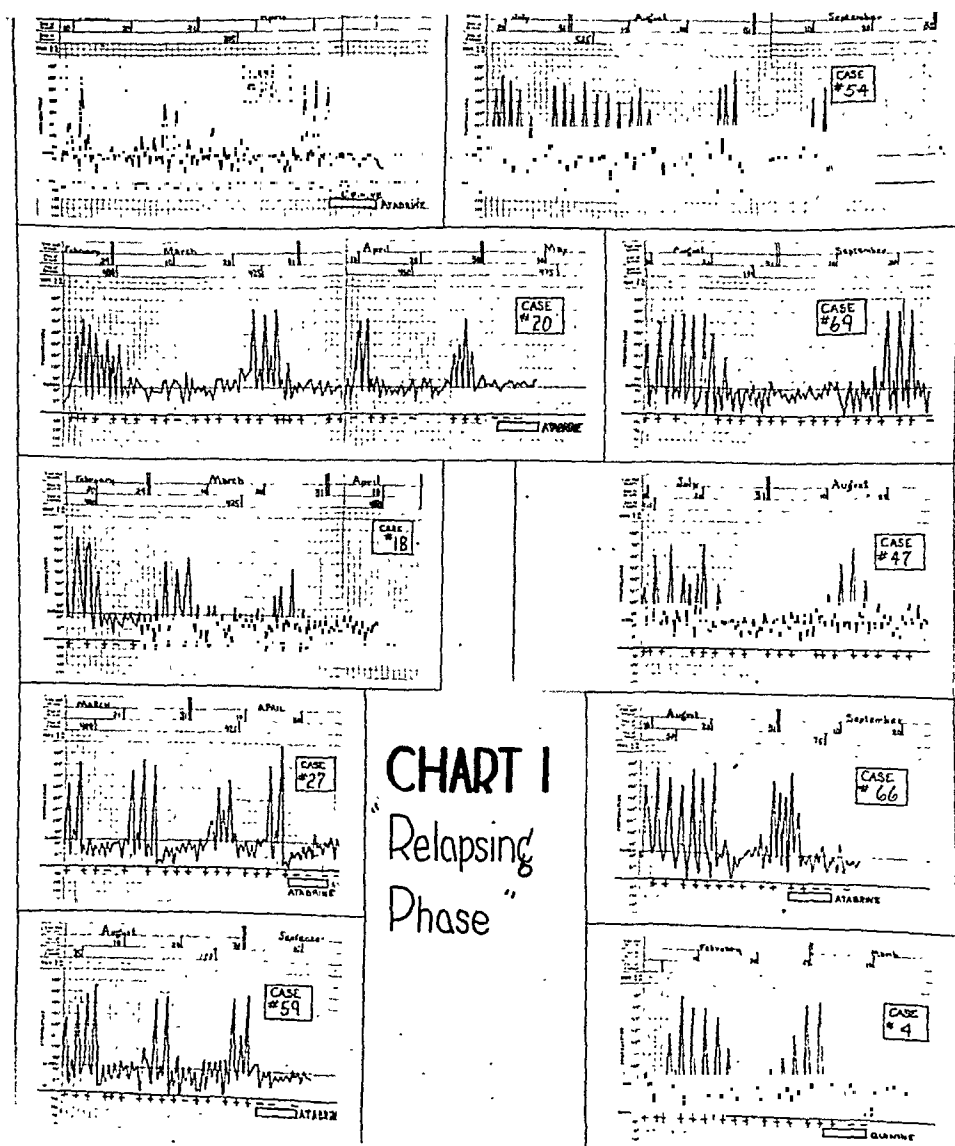


CHART 1

of all relapses occurring within 90 days. The remaining 2.2% of the relapses occurred between the 90th and 187th days. Actually, therefore, the pattern of relapsing Southwest Pacific malaria, with periodic relapses, is not characteristic of the natural course of the disease, but is characteristic of symptomatic drug therapy which produces only temporary clinical suppression.

As regards the total duration of the disease, it is evident that it may require 2 or more years to run its course once the phase of chronic relapse has become estab-

lished, but it must be remembered that the cases we have studied may have had their clinical courses altered by previous therapy overseas. It cannot be positively stated that periodic drug therapy prolongs the course of the disease, but it certainly does not shorten it, and the studies which we have carried out strongly suggest that immunity and cure may come earlier if drug therapy is withheld. As a possible aid in determining this point, complement fixation tests for malaria were carried out weekly on the blood of these patients. However, the results

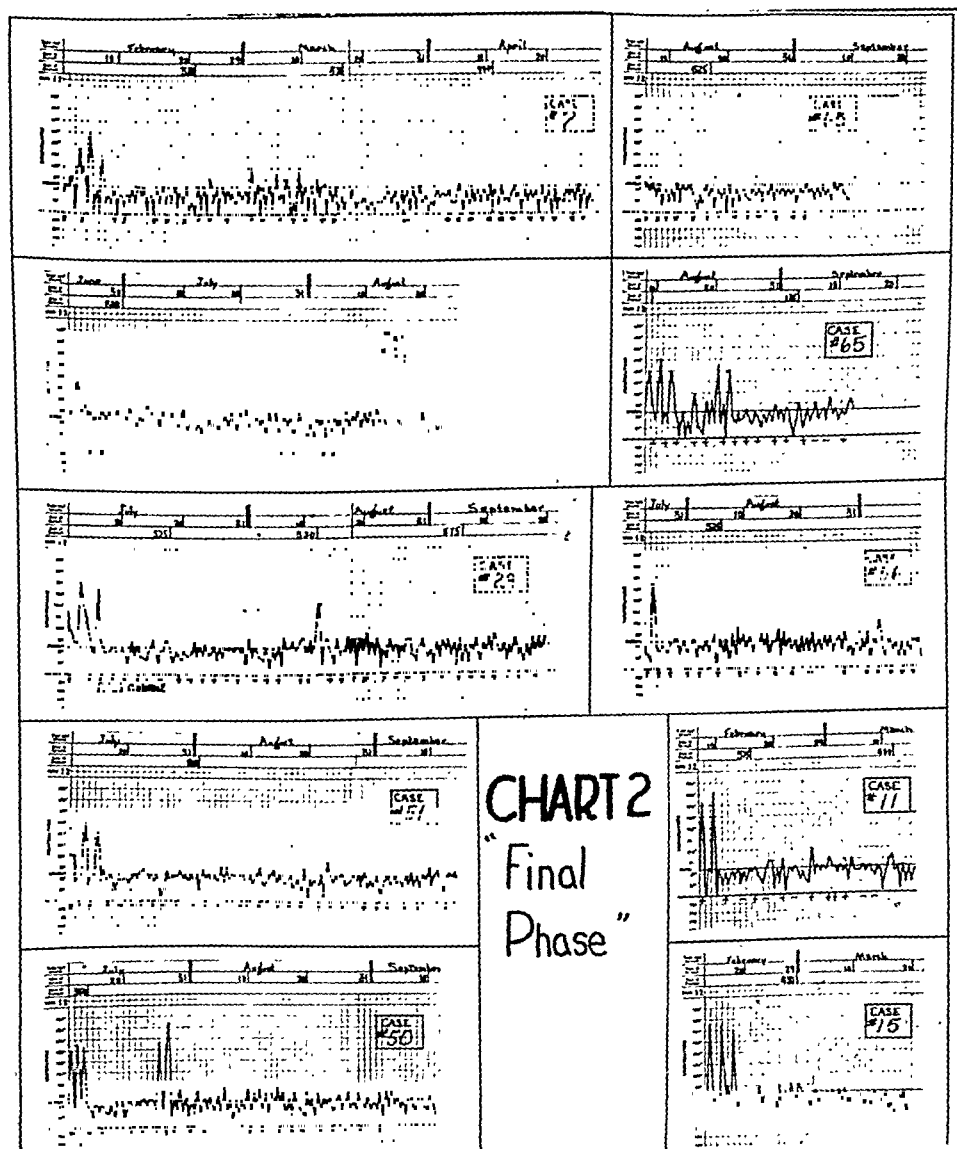


CHART 2

were too inconsistent to be a satisfactory guide in prognosticating either cure or subsequent relapse.

Whether or not the course of the disease would be greatly shortened by withholding therapy from the very onset could only be determined by initiating a program similar to ours overseas, and carrying out a prolonged follow-up study. The cases which have been continually suppressed clinically overseas by drug therapy and who first become ill after their return to this country when this drug has been withdrawn, may ultimately run the complete course of the disease as suppressive therapy may only have deferred the clinical onset, and not affected any reduction in its ultimate duration once it has started.

Summary. 1. The natural course of untreated chronic Southwest Pacific vivax malaria has been observed in 72 patients.

2. Our observations indicate that there are 3 phases of the disease: (1) an initial phase, characterized by irregular fever, often occurring daily; (2) an intermediate chronic relapsing phase, usually characterized by irregularly occurring "bouts" of fever, tertian in type, and parasitemia; and (3) a late or terminal phase which is subclinical and is characterized by irregularly appearing parasitemia.

3. As the development of immunity and presumably cure in chronic malaria apparently takes many months when drug therapy is withheld, "non-specific" therapy is an impracticable therapeutic procedure.

4. The frequently encountered cyclic periodicity of relapse in chronic Southwest Pacific malaria is apparently due to the drug therapy (atabrine) of the acute attack, and very rarely occurs without treatment.

REFERENCES

1. BOYD, M. F., and KITCHEN, S. F.: Renewed Clinical Activity in Naturally Induced Vivax Malaria, *Am. J. Trop. Dis.*, **24**, 221, 1944.
2. (a) CECIL, R. L.: *A Textbook of Medicine*, Philadelphia, Saunders, p. 430, 1940. (b) MANSON-BAHR, P. H.: *Manson's Tropical Diseases*, Baltimore, Williams & Wilkins, p. 53, 1940. (c) STRONG, R. P.: *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases*, Philadelphia, Blakiston, p. 1, 1943.
3. SAPHIR, O.: *An Outline of Tropical Medicine*, Chicago, Michael Reese Research Foundation, pp. 56 to 65, 1944.

ELECTROCARDIOGRAPHIC EVIDENCE OF CARDIAC COMPLICATIONS IN INFECTIOUS MONONUCLEOSIS*

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IN the course of an epidemic of infectious mononucleosis in which upwards of 100 cases were observed, there were a few in which the heart apparently became involved. Our interest was first aroused when, during the clinical study of a patient presenting a problem in differential diagnosis, an electrocardiogram revealed T wave changes strongly suggesting pericardial involvement. This finding became of more than passing interest when it was later shown that the patient had infectious mononucleosis. Insofar as we are aware there have been few reports on infectious mononucleosis mentioning cardiac complications and none have included cases similar to those now to be described. The absence of fatal cases makes the problem impossible to study in autopsy material.

Case Reports. CASE 1. W. R. P., a sailor 20 years of age, was admitted to the Dispensary on Oct. 3, 1944, complaining of fever and headache. Except for mild pleurisy at the age of 15, he had always been unusually well and robust until 2 days before admission when he developed the usual symptoms of gripe. At the time of entry, the body temperature was 99.4° F., the pulse rate was 60, and the respiratory rate was 20 a minute. Examination revealed no abnormality save for signs of nasopharyngitis. The heart was not enlarged, the sounds were of good quality, and no murmurs were heard. The blood pressure was 122 mm. Hg systolic and 76 diastolic.

He responded well to simple treatment for gripe until the 3rd day when his condition suddenly worsened. The temperature rose to 103.4° F. and the pulse rate to 96. The cervical and epitrochlear lymph glands were found to be enlarged. Examination of the

blood revealed no anemia and the leucocyte count was 9650 (53% granulocytes, 46% lymphocytes, and 1% monocytes). Urinalysis was negative save for 1+ albumin.

On the 4th day there was pain in most of the large joints of the extremities and on the 5th day the joint pains were severe. A sparse, macular rash, confined to the trunk, appeared on this day and there was a non-productive cough. Differential diagnosis included: (1) infectious mononucleosis, (2) endemic typhus, (3) cerebrospinal fever, and (4) rheumatic fever.

On the 7th day the patient was acutely ill, the temperature rising to 104.8° F., at which time the pulse rate was 96. He was mentally confused and there was moderate stiffness of the neck. There was no apparent change in heart size, the sounds were of good quality, and no murmurs were heard. The electrocardiogram showed low or diphasic T waves in all leads. There was no significant change in the blood findings. The sedimentation rate was 17 mm. in 1 hour. On the 9th day radiologic examination of the chest revealed no abnormality except that the heart was slightly larger than previously. Agglutination tests for endemic typhus, brucella abortus, and the typhoid group were negative.

The patient remained severely ill until the 13th day when he began to improve; the joint pains were less severe and the rash was fading. Radiologic examination still showed the heart to be enlarged and the electrocardiogram revealed slight inversion of the T waves in Leads I and IVF. On the 15th day the leucocyte count was 5900 with 68% lymphocytes, some of which were immature forms. The Paul-Bunnell test was positive in a dilution of 1:56.

The patient gained in strength and well-being, and on the 18th day was allowed out

* The views represented in this paper are those of the authors and do not necessarily reflect those of the Navy Department.

of bed. On this day the percentage of lymphocytes had risen to 74, with an increase in the number of immature forms, and the Paul-Bunnell test was positive in 1:224 dilution. The diagnosis of infectious mononucleosis now seemed certain. Convalescence was slow, but uninterrupted. On the 20th day radiologic examination showed that the

heart had returned to its original size. The T waves in the electrocardiogram were still abnormally low in Leads I and II. The Paul-Bunnell test was positive in a dilution of 1:448, and remained so for a period of 3 weeks. He was returned to duty in good health Nov. 25, 1944, and was well and strong when last examined May 30, 1945.

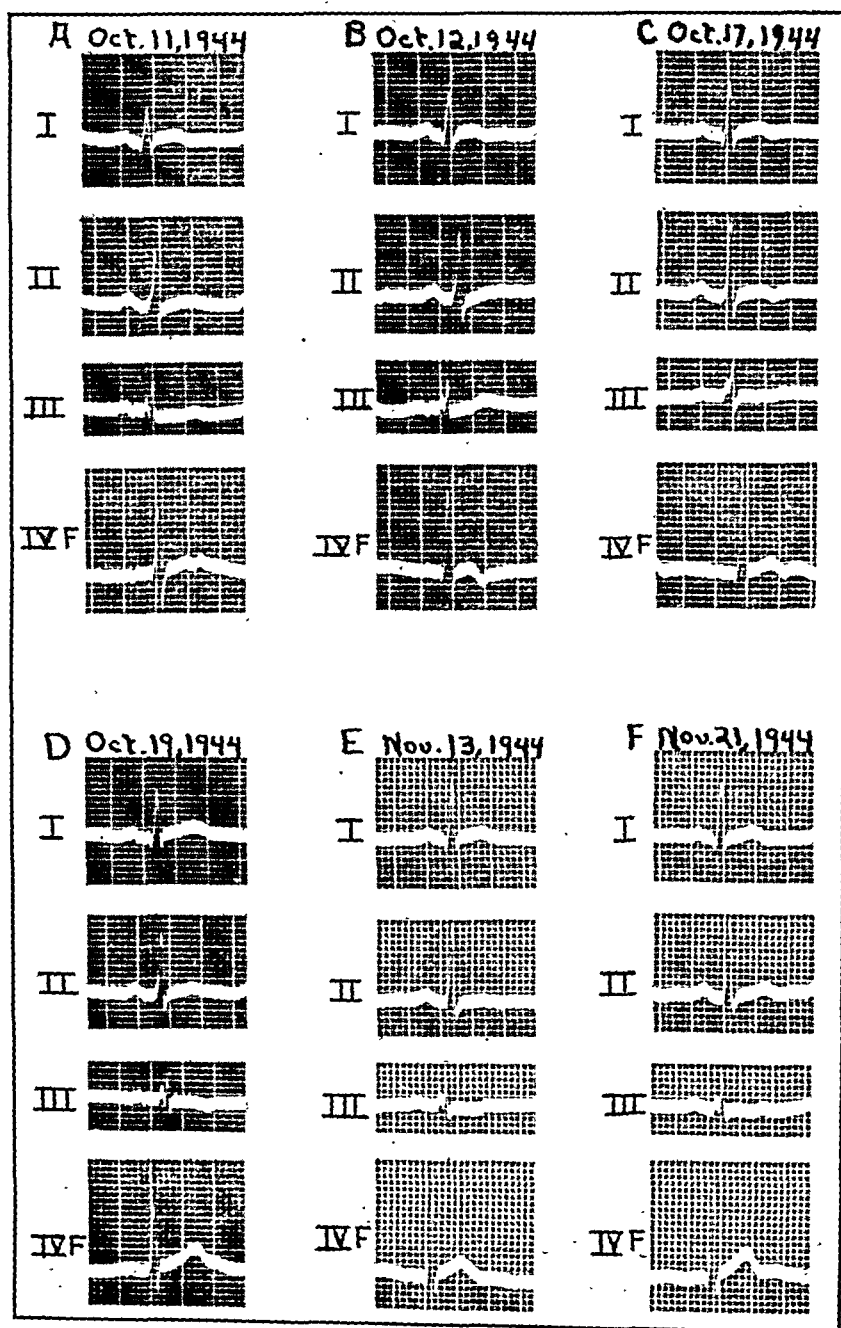


FIG. 1.—Showing serial electrocardiograms in the case of W. R. P. A shows low T waves in the limb leads and a notching of T in IVF. In B and C the T waves are low or inverted in all leads. In D, E and F there is a gradual return toward the normal.

A series of 22 electrocardiograms was taken throughout the period of illness and convalescence, and portions from 6 representative tracings are shown in Figure 1, A-F. There are changes in the amplitude of QRS, but the striking changes are the progressive lowering or inversion of the T waves in all leads with slow but eventual return toward the normal.

CASE 2. J. L. T., a naval aviator 24 years of age, was active and well until Oct. 30, 1944, when he developed headache and malaise. Examination was essentially negative except for signs of nasopharyngitis. He did not respond favorably to symptomatic treatment and on the 3rd day was admitted to the Dispensary. The body temperature was 103.8° F., the pulse rate was 82, and

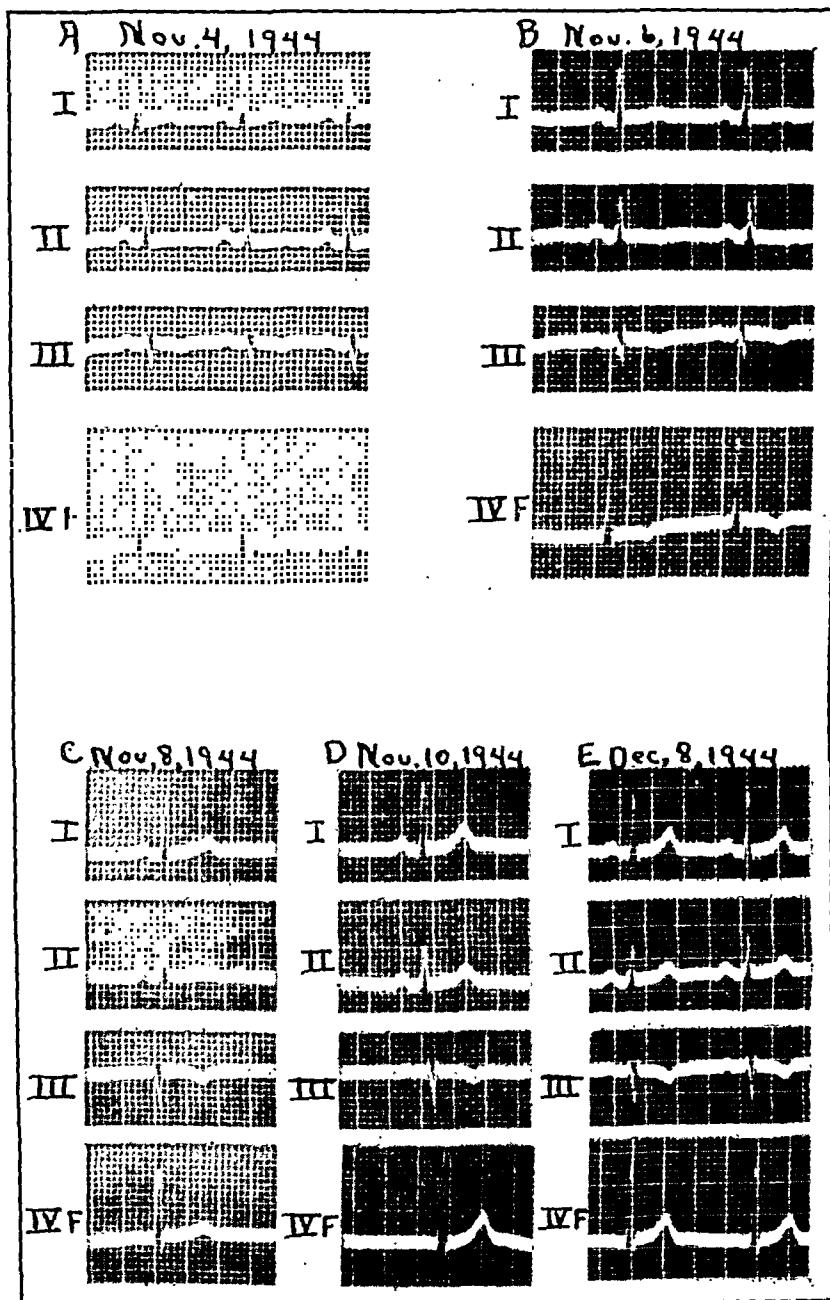


FIG. 2.—Showing serial electrocardiograms taken in the case of J. L. T. A was taken on the 5th day of illness and shows low or inverted T waves in all leads. The T waves remain low or inverted in B. C, D and E show a progressive return to the normal.

the respiratory rate 20. Examination revealed a very well developed person acutely ill. There were signs of inflammation of the nasopharynx, injection of the sclerae, and lacrimation. A sparse, maculo-erythematous rash was present over the trunk and thighs. There was moderate enlargement of the cervical lymph glands. The heart was not enlarged, the sounds were of good quality, and no murmurs were heard. The blood pressure was 126 mm. Hg systolic and 84 diastolic. The differential diagnosis included: (1) endemic typhus, (2) infectious mononucleosis, (3) measles, and (4) cerebrospinal fever. On the 4th day (2nd day of admission) the rash was extensive over the trunk and

thighs. Examination of the blood revealed no anemia, the leucocyte count was 6400 (77% granulocytes, 22% lymphocytes, and 1% monocytes). Radiologic examination of the chest revealed no abnormality.

On the 5th day the patient complained of pain in the joints of the extremities, and tenderness of the muscles in forearms and calves. He was restless, nauseated, and mentally confused. The temperature was 102.4° F. and the pulse rate 80. The heart had not increased in size, but a slight friction rub was heard to the left of the sternum in the 4th interspace. An electrocardiogram taken on this day (Fig. 2, A) shows low or inverted T waves in all leads. Examination

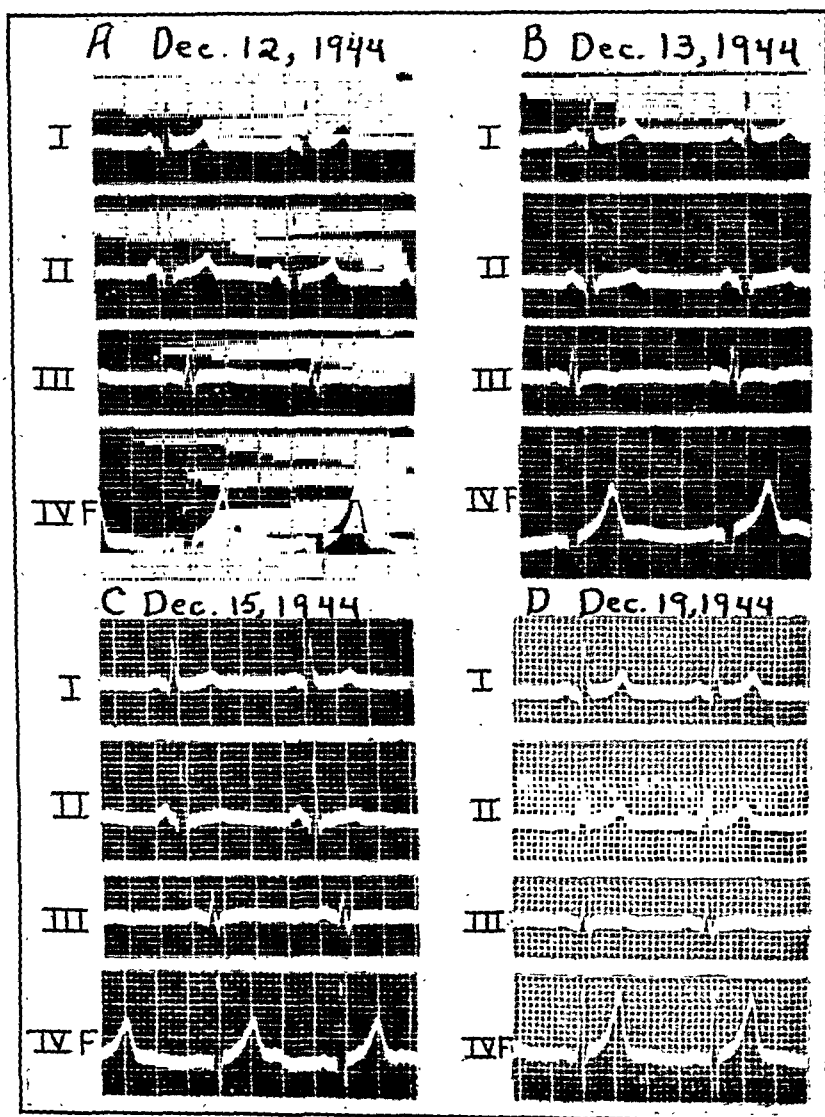


FIG. 3.—Showing electrocardiograms in the case of A. B. The electrocardiogram in A was taken on the 2nd day of illness and shows no definite abnormality. There is progressive lowering of T_1 and T_2 in B and C with a return to normal in D.

of the blood revealed no change except for the presence of a number of immature lymphocytes. The Paul-Bunnell test was positive in 1:112 dilution. A definite diagnosis was made of infectious mononucleosis, with involvement of the pericardium.

The patient remained severely ill until the 7th day, when he began to improve and subsequent recovery was uneventful. The rash and joint pains gradually disappeared, the temperature fell to normal, and the pulse rate decreased to 60. The Paul-Bunnell test became positive in a dilution of 1:224, and the percentage of lymphocytes increased to 45, with many immature forms. Serial electrocardiograms (Fig. 2, A-E) show a progressive change in the T waves from the abnormal to the normal. The patient returned to duty Nov. 21, 1944, feeling well. He was healthy and strong when last seen on May 26, 1945.

CASE 3. A. B., a chief petty officer 34 years of age, was admitted to the Dispensary on Dec. 11, 1944, complaining of pain in the chest. He had been in good health until 24 hours before admission when he noticed pain in the lower portion of the left lateral chest wall which was aggravated by respiration. Physical examination revealed a well developed person. The body temperature was 98.6° F., the pulse rate was 84, and the respiratory rate 15. Over the trunk there was a sparse, maculo-erythematous rash. The cervical lymph glands were enlarged. A few fine moist râles were heard over the base of the left lung. The heart was not enlarged, the sounds were of good quality, and no murmurs were heard. The blood pressure was 122 mm. Hg systolic and 78 diastolic. The examination of the blood revealed no anemia. The leucocyte count was 15,800 (61% neutrophils, 33% lymphocytes, and 6% eosinophils). Blood taken for a Paul-Bunnell test was later reported positive in a dilution of 1:224. Radiologic examination of the chest revealed no abnormality of heart or lungs. A diagnosis was made of infectious mononucleosis.

On the 3rd day there was no significant change in the symptoms or physical signs. An electrocardiogram taken this day (Fig. 3, B) shows slight but definite lowering of the T waves in the limb leads. The Paul-Bunnell test was positive in a dilution of 1:896.

The subsequent clinical course was that

of a mild illness. The fever was never greater than 100.6° F. (on the 6th day). The pulse rate ranged from 68 to 100. The rash began to fade on the 5th day and disappeared on the 7th day. Joint pains subsided with the rash. The highest percentage of lymphocytes was 51, with a moderate number of immature forms. Repeated radiologic examination of the heart and lungs revealed no abnormal findings. An electrocardiogram taken on the 4th day (Fig. 3, C) shows abnormally low T waves in Leads I and II, but a record obtained on the 8th day (Fig. 3, D) shows normal T waves.

CASE 4. S. M. E., a naval aviator 23 years of age, entered the Dispensary June 5, 1945, complaining of headache and fatigue. Within the course of a few days he presented the characteristic clinical and laboratory findings of glandular fever. There was malaise, fever (103° F.), and generalized lymphadenopathy; the Paul-Bunnell test was positive in dilutions as high as 1:3584 and the blood smear showed 86% lymphocytes, some of which were immature forms. Examination of the heart revealed no abnormality except that the heart sounds heard at the mitral area decreased in intensity at the height of the illness. At no time was there rash or joint pains. Serial electrocardiograms were taken which show (Fig. 4, A, B and C) a progressive lowering of the T waves in Leads I, II, and IVF with gradual return to the normal.

In addition to the above 4 cases, there were a few others in which there were slight but definite electrocardiographic changes at the height of the illness. Also, there was 1 case of pericarditis with massive effusion in which the only etiologic diagnosis possible was infectious mononucleosis.

An aviation cadet, 20 years of age, was well and strong until 3 weeks previously when he first noticed a "catch" in the chest on taking a deep breath. Within a few days he complained of occasional twinges of pain radiating from the mid-sternum across the left chest and a slight non-productive cough developed. Three days prior to admission he was forced to discontinue sports and subsequently complained of malaise, anorexia, and dyspnea. At the time of examination, he appeared ill. The body temperature was 101.5° F. and the pulse rate 120 a minute. The heart was moderately enlarged, the sounds were of poor quality, and a friction rub was heard

in the 3rd and 4th intercostal spaces to the left of the sternum. The blood pressure was 150 mm. Hg systolic and 102 diastolic. There were no congestive phenomena. While the electrocardiogram was being recorded, the patient declared that he felt sick, and within a few seconds the radial pulse could not be felt. He responded to treatment for shock and was sent to the hospital with the diagnosis of pericarditis with effusion, possibly of rheumatic origin.

of coëxistent rheumatic fever was considered but thought to be unlikely since the onset was not preceded by a respiratory infection, the joints were never involved, the response to salicylates was unfavorable, and no cardiac murmurs were heard. Lacking positive evidence for any additional diagnosis, it was thought that the pericarditis was probably a complication of the infectious mononucleosis.

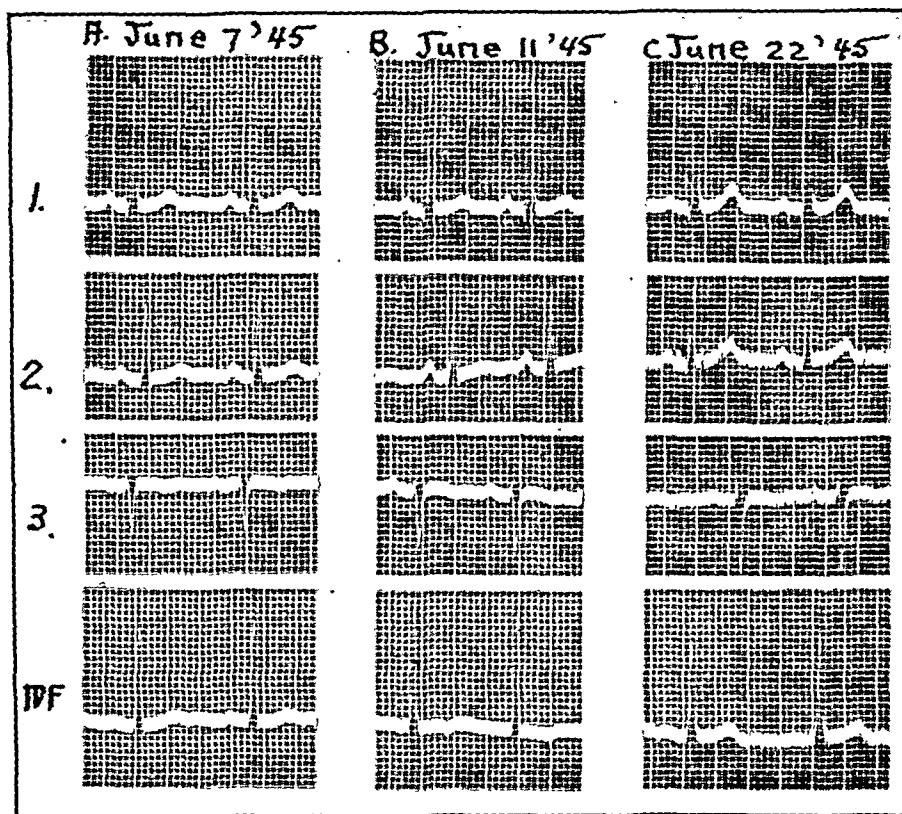


FIG. 4.—Showing serial electrocardiograms in the case of S. M. E. A and B were taken at the height of illness and show abnormally low or slightly inverted T waves in all leads. In C, the T waves are within normal limits.

We are indebted to Captain Jesshill Love, (MC) USNR, for information regarding the course of the patient's illness. Comprehensive studies, including examination and culture of pericardial fluid on several occasions, were undertaken in order to establish an etiologic diagnosis. The only definite finding was a positive Paul-Bunnell test in dilutions as high as 1:896. The percentage of lymphocytes increased from 21 to 59. The T waves of the electrocardiogram became moderately low in the limb leads and became diphasic in Lead IVF. The possibility

Discussion. The above 4 case reports are offered as proof that, in occasional patients with infectious mononucleosis, the heart may become affected. These patients presented the clinical and laboratory findings characteristic of infectious mononucleosis. It is of interest that in 3 of the 4 patients, involvement of the heart was detected shortly after the appearance of an erythematous rash and joint pains.

There is some evidence that the cardiac involvement was more of the pericardium

than of the myocardium. In Case 1, the T wave changes not only are characteristic of pericardial involvement but persisted over a longer period of time than would be expected if the myocardium alone was affected; long after the patient was apparently well, the T waves remained abnormally low in amplitude. In Case 2, a friction rub was heard and the T wave changes are consistent with pericarditis. In Case 3, the illness was not severe and it seems unlikely that the heart muscle was sufficiently affected to produce the electrocardiographic changes found. In Case 4, the only definite evidence of cardiac involvement was the electrocardiographic changes which resembled those in the other cases.

The heart rate was slow relative to the body temperature in Cases 1 and 2; there was evidence of central nervous system involvement in these cases which may have been a factor. In no instance was there evidence of congestive failure. The heart sounds in most cases remained good throughout the entire illness.

Bernstein,¹ in his monograph on infectious mononucleosis, states that cardiac disturbances are unusual in this disorder but that certain sequelæ have been reported which indicate that there may be involvement of the heart during an attack. This author refers to isolated reports^{2,3} of valvular deformity following glandular fever and not only considers the possibility that rheumatic fever may have been present as a complication but that valvular

injury may result in uncomplicated cases of infectious mononucleosis. The first named possibility was strongly considered in 2 of our cases early in the disease but there were good grounds for believing that rheumatic fever was never present.

Longcope⁴ reported the appearance of ventricular extrasystoles in 1 of the patients of his series but observed no other electrocardiographic abnormalities. There were no cardiac arrhythmias observed in any of the cases studied by us.

Summary and Conclusions. 1. Four cases of infectious mononucleosis with cardiac complications have been presented. Additional cases are mentioned in which the same complications were possibly present.

2. The diagnosis of infectious mononucleosis was confirmed in each instance by the characteristic clinical and laboratory findings seen in this disease.

3. Rheumatic fever may have to be included in the differential diagnosis. In 3 patients, in addition to the usual symptomatology, an erythematous rash appeared associated with joint pains.

4. In all 4 cases there were alterations in the electrocardiogram; in 1, there was slight cardiac enlargement; and in 1 other, a friction rub was heard.

5. The evidence suggests that the cardiac involvement was mainly pericardial.

6. It is concluded that occasionally there may be cardiac complications in infectious mononucleosis.

REFERENCES

1. BERNSTEIN, A.: *Medicine*, 19, 95, 1940.
2. BRADSNOW, R. W.: *Ohio State Med. J.*, 27, 717, 1931.
3. DuBOISE, A. H.: *Acta med. Scandinav.*, 73, 237, 1930.
4. LONGCOPE, W. T.: *AM. J. MED. SCI.*, 164, 781, 1922.

THE TREATMENT OF HUMAN HYPERTENSION WITH A KIDNEY EXTRACT*

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THE treatment of hypertension with kidney extracts and the rationale of such therapy have been reviewed recently.^{2,3,8} Favorable therapeutic results have been attributed respectively, to renin,¹⁴ to angiotoninase (hypertensinase),¹⁰ and to unspecified⁶ or non-specific¹² factors present in these extracts. This paper reports the treatment of a small, carefully controlled series of hypertensive patients with a kidney extract which contained no renin or angiotoninase activity.

Kidney extracts were prepared by methods described in the literature^{4,9} and were assayed in hypertensive rats and dogs. Modifications of these methods were made with a view to decreasing the toxicity and solids content of the extract without any considerable loss in blood pressure-lowering activity. In this way a concentrated extract was produced which assayed favorably in rats and dogs and was of relatively low toxicity. This extract was prepared in batches and pooled for treatment of a group of hypertensive patients.

Preparation of the Extract. Kidney extract was prepared from fresh hog kidneys which were minced with ice, treated with monoethanolamine, acidified with HCl, heated briefly,⁹ and fractionated with ammonium sulfate. The material used was soluble in 3% trichloroacetic acid from which it was

precipitated by saturation with ammonium sulfate. The entire procedure, with the exception noted above, was carried out in the cold.

The 1700 ml. of extract (containing merthiolate 1:10,000) obtained from 725 lbs. of kidneys were pooled and stored in sterile vials in the refrigerator.

Fractionation of the extract was accomplished by first diluting with 7 volumes of water. The precipitate (fraction 1) was discarded. Ammonium sulfate was added to a final concentration of 30%. The resultant precipitate (fraction 2) was dissolved in water, dialyzed and concentrated. This material, containing merthiolate 1:10,000, is the fraction which was administered to Cases 1 and 3. Materials precipitated at 40 to 100% saturation with ammonium sulfate were combined as fraction 3.

Limitations of space preclude full presentation of the method.

Properties of the Extract. Composition. The extract was a slightly opalescent amber liquid which jellied in the refrigerator. It had a pH of 6.5 and a density of 1.01. It contained 5.9% solids, 0.98% total nitrogen and 0.34% NPN (soluble in 5% trichloroacetic acid) by Kjeldahl analysis.

Enzyme Content.§ The angiotonin activity of a standard angiotonin solution, assayed by injection into the abdominal aorta of normal rats,⁵ was not diminished significantly following incubation with the extract in saline at pH 5 or 7. No renin activity (pressor response) was found on injection

* A preliminary report was presented at the 74th meeting of The Society of Clinical Surgery at Cincinnati, April 3, 1942.

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§ Dr. Page kindly confirmed the absence of angiotoninase and renin activity from our extract while Dr. Kemp of his laboratory confirmed the blood pressure-lowering activity of the extract in hypertensive rats.

of the extract intravenously into normal dogs and rats, though doses of 2 ml. per kg. gave small transient reductions in blood pressure in anesthetized hypertensive dogs. No amylase, proteolytic, or lipolytic activities were found in the extract.

Toxicity. Intravenous injection of 15 ml. of extract/kg. body weight in rabbits, 20 ml./kg. in mice, and 3 ml./kg. in a monkey produced no noticeable reactions. Intravenous injections in hypertensive (silk) rats lowered their blood pressures (tail cuff technique) and raised their rectal temperatures.

Ten mice, 10 rats, 10 guinea pigs and 5 rabbits were given intramuscular injections of 0.2 ml./kg. daily for 37 days. Equal numbers of animals were similarly injected with distilled water. Sections of heart, liver, spleen, pancreas, kidney and other tissues showed no more pathologic change than the controls. Anaphylactic reaction in guinea pigs could be produced by the extract but was not elicited by the series of 37 daily injections.

Forty patients seen regularly in the Allergy Clinic were given intradermal injections of the extract, which elicited no positive reactions.

times by 2 different observers; many readings were taken at each visit and 3-day running averages have been charted in the accompanying illustrations. Patients were given the routine hospital diet without restriction of salt. No sedatives were given.

Daily treatment was prolonged until no favorable response was being obtained, or until reactions necessitated stopping the extract.

Case Histories. CASE 1. B. G. (Fig. 1) was a 50 year old colored female, who was first told she had an elevated blood pressure in 1934. In 1936, her blood pressure ranged from 230-200/140-120. With limitation of activity she improved somewhat.

When admitted for treatment with extract she had slight cardiac enlargement, hypertensive retinopathy (Grade 3), ECG evidence of left ventricular strain, normal urinary dilution-concentration range, and normal BUN. Urea clearance, 70% of normal, remained unchanged during treatment. Retrograde pyelograms showed no abnormalities. After 14 days in the hospital, kidney extract was administered for 28 days. On the 28th hospital day urticaria and a generalized erythematous rash with itching were

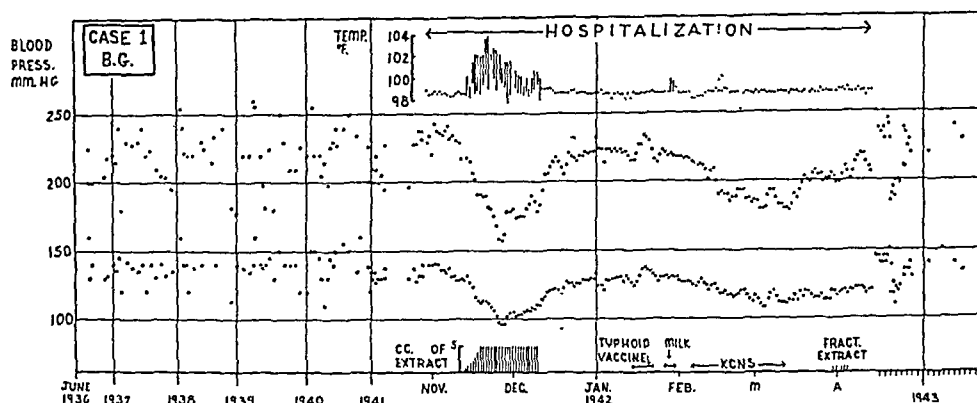


FIG. 1.—Blood pressure, body temperature and therapeutic schedule of Case 1.

Clinical Trial. The extract was administered to 4 hypertensive patients; 3 had been under observation for long periods; a fourth, with malignant hypertension, was selected because some reports noted striking improvement in cases of this type.

Patients were hospitalized on the Medical Service of the Cincinnati General Hospital for 14 to 26 days before treatment was begun. Blood pressure readings were taken twice daily after 1 hour bed rest at appointed

first observed. On the 42nd hospital day local reactions became so pronounced that treatment was discontinued.

On the 45th day the patient's serum gave a positive precipitin test with a 1:1000 dilution of whole extract. By the 63rd day the titer had declined to 1:5 and was the same on the 148th day. The second fraction of the original extract, for which the patient had no precipitins, was given for 6 days

beginning on the 152nd day; no reactions were noted.

CASE 2. E. H. (Fig. 2), a 46 year old white female, a known hypertensive since 1938, was admitted to Cincinnati General Hospital in 1940 because of hypertensive encephalopathy. A bilateral lumbar splanchnicectomy was done. Her blood pressure showed no significant change after operation, although some symptoms were improved.

CASE 3.—R. S. (Fig. 3), a 27 year old colored female, was first found to have hypertension in 1939. On admission in 1942 she had slight enlargement of the left ventricle and her eyegrounds showed mild arterial constriction. The ECG, dilution-concentration, urea clearance and pyelograms were normal. On the 26th hospital day kidney extract was begun. Mild urticaria and angioneurotic edema were noted on the

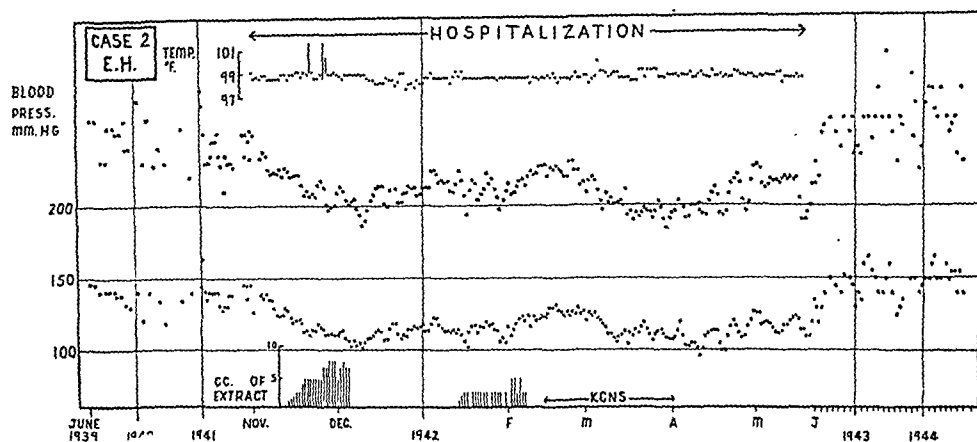


FIG. 2.—Blood pressure, body temperature and therapeutic schedule of Case 2.

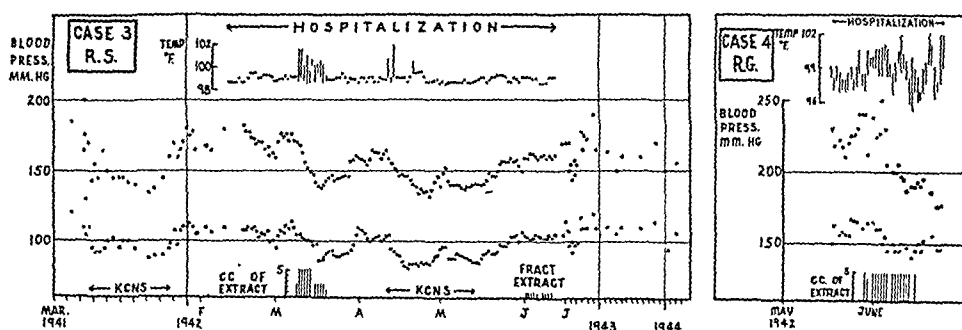


FIG. 3.—Blood pressures, body temperatures and therapeutic schedules of Cases 3 and 4.

On admission in 1941, examination showed moderate cardiac enlargement, evidence of diffuse cerebral vascular disease, hypertensive retinopathy (Grade 3), normal PSP and dilution-concentration tests. Her urea clearance, 40% of normal, remained fixed during treatment. Intravenous pyelograms were normal. Kidney extract was begun on the 14th hospital day and stopped on the 36th hospital day because of poor response. During this period there was no appreciable change in her physical state. Six weeks later, skin tests with the whole extract were still negative, and the same extract was again injected without affecting her symptomatology.

34th hospital day; increase in these symptoms necessitated discontinuation of the injections. On the 35th and 43rd hospital days the patient's serum gave a positive precipitin test with a 1:5 dilution of the whole extract. On the 122nd day the precipitin titer was 1:10.

Beginning on the 111th hospital day she was treated with the second fraction of kidney extract to which she gave no reaction on intradermal injection. No effects were noted.

CASE 4.—R. G. (Fig. 3), a 36 year old colored female, first noted progressive exertional dyspnea 4 mos. prior to hospitalization. Orthopnea, paroxysmal nocturnal

dyspnea, and mild ankle edema appeared about 2 weeks before entering the hospital.

Examination on admission disclosed papilledema, retinal hemorrhages and exudate, and marked arteriolar constriction. Findings of congestive failure were present. Albumin, many pus cells, and small numbers of casts were found in the urine. The BUN rose from 33 to 150 mg. % during hospitalization.

Extract was started on the 12th hospital day and continued for 16 days. Progressive weakness, Cheyne-Stokes respiration, increasing edema, and delirium were observed during this time. The patient died in uremic coma on the 40th hospital day.

Summary of Clinical Observations.

Blood Pressure. All 4 patients showed some fall in blood pressure following treatment with kidney extract as indicated in the accompanying graphs. This was more striking in the systolic than in the diastolic level. The change in blood pressure was undoubtedly associated with the use of kidney extract, with the possible exception of Case 4.

Symptoms. All patients complained of various symptoms associated with hypertension, most of which remained unchanged during hospitalization.

Fundus Oculi. No significant retinal changes were noted during the hospital period.

Toxic Reactions. Remittent fever was the most commonly observed toxic reaction. Injections of the extract were given in the morning and the temperature peaks followed in the late afternoon. Lethargy and anorexia accompanied the markedly febrile periods. Slight leukocytosis was observed in 1 case (R. S.), and 2 patients showed a slight weight loss during the treatment period.

Skin tests and allergic history of each patient were initially negative. Despite this, 2 subjects developed urticaria and mild angioneurotic edema on the 10th and 15th days of treatment, which disappeared in a few days although treatment was not stopped.

Local reactions, consisting of pain and heat and redness of the skin overlying

the injected area were observed to a varying degree in each case. In 2 subjects (B. G., R. S.) their severity necessitated discontinuation of treatment.

The fall in blood pressure during thiocyanate administration⁷ was of the same magnitude as that following kidney extract in 2 cases (R. S., E. H.) but was not as marked in the other patient. Thiocyanate did not induce the febrile response seen during kidney extract injections.

Discussion. The method of preparing this kidney extract, while similar to published methods,^{4,9,11,12} differs from them in several respects, including an initial alkaline extraction and a final precipitation with trichloroacetic acid. Alkalies help dissolve kidney tissue and monoethanolamine was particularly useful in this respect. Trichloroacetic acid removed renin, angiotoninase and other enzymes.

Some investigators have suggested that renin or angiotoninase is responsible for the blood pressure lowering activity of kidney extracts. While a fall in blood pressure may accompany injection of these enzymes it may also occur in their absence as shown by our results. It remains to be seen whether these enzymes are active in pure form.

It has also been suggested that the blood pressure lowering activity of kidney extracts arises from their pyrogenic activity, as in the case of pyrogenic insulin, tyrosinase, typhoid vaccine, etc. Since the depressor effect in our patients appeared coincident with fever, the fall in blood pressure might be attributed to the elevated temperature, although blood pressure measurements made during the afternoon peak of the fever were not appreciably lower than those made in the morning before the temperature began to rise. This is at least suggestive that vasodilatation alone was not responsible for the depressor effect. Other unknown factors, possibly renal hyperemia as suggested by Chasis *et al.*,¹ may be operative in producing this effect.

It is possible that allergic or toxic effects played some part in the lowering of the

blood pressure. Although reactions were never observed immediately after injection, various allergic phenomena (local reactions and urticaria) appeared later in 2 subjects, coincident with the greatest fall in blood pressures. The reactions we observed were similar to the initial mild reactions described by Schales, Stead and Warren.¹²

There is an interesting possible correlation between development of serum precipitins and the clinical effectiveness of the extract which suggests that more intensive study of this aspect may be desirable. Cases 1 and 3 had the most pronounced fall in blood pressure, and this fall coincided with the theoretical onset of maximum antibody production. This is confirmed insofar as precipitin tests were made. Furthermore, the non-antigenic fractions administered in Cases 1 and 3 had no effect. No precipitin tests were done with serum from Case 3 whose skin tests were uniformly negative.

Our subjects did not exhibit a favorable symptomatic response such as others have reported. No appreciably objective change was observed in the eyegrounds or in cardiac or renal function. No decrease in

the hemoglobin level, similar to that reported by Page *et al.*¹⁰ was observed, although our cases were treated for considerably shorter periods.

Conclusions. 1. The preparation and properties of a kidney extract used in the treatment of human and animal hypertension are reported. This extract contained no demonstrable angiotoninase or renin and was of relatively low toxicity in animals.

2. Four hypertensive patients were treated parenterally with this extract. Three of them showed during treatment a noteworthy fall in blood pressure, associated with fever. The fourth patient who developed little fever, demonstrated only a slight depressor effect.

3. The 2 subjects who demonstrated the greatest fall in blood pressure exhibited hypersensitivity reactions and developed serum precipitins.

4. The results obtained with this kidney extract in the treatment in human hypertension do not recommend its use. Until the toxic effects of such kidney extracts can be eliminated, their therapeutic evaluation will be difficult and the mechanism of their action undetermined.

Details of the preparation of the kidney extract and case histories are available on request to the authors.

Dr. Virgil Hauenstein and Dr. Arthur Freedman of the Cardiac Laboratory assisted with the clinical aspects of the work. Dr. A. G. Wedum of the Dept. of Bacteriology performed the precipitin tests. Dr. P. M. Zeek of the Dept. of Pathology performed the pathologic examinations. Mr. Henry Block and Miss Lucille Keifer assisted with certain chemical analyses. Dr. Irvine Page furnished the angiotonin solution. Various amines were supplied by Carbide and Carbon Chemicals Corporation.

REFERENCES

1. CHASIS, H., GOLDRING, W., and SMITH, H. W.: *J. Clin. Invest.*, **21**, 369, 1942.
2. GOLDBLATT, H., LEWIS, H. A., and KAHN, J. R.: *Nelson Loose-Leaf Medicine*, New York, Thomas Nelson & Sons, p. 163, 1943.
3. GOLDRING, W., and CHASIS, H.: *Hypertension and Hypertensive Disease*, New York, Commonwealth Fund, 1944.
4. GROLLMAN, A., WILLIAMS, J. R., JR., and HARRISON, T. R.: *J. Biol. Chem.*, **134**, 115, 1940.
5. GROSSMAN, E. B., and WILLIAMS, J. R., JR.: *Arch. Int. Med.*, **62**, 799, 1938.
6. HARRISON, T. R., GROLLMAN, A., and WILLIAMS, J. R., JR.: *Trans. Assn. Am. Phys.*, **57**, 187, 1942.
7. KOTTE, H.: *Ohio State Med. J.*, **39**, 20, 1943.
8. PAGE, I. H., and CORCORAN, A. C.: *Arterial Hypertension, Its Diagnosis and Treatment*, Chicago, Year Book Publ., 1945.
9. PAGE, I. H., HELMER, O. M., KOHLSTAEDT, K. G., FOUTS, P. J., and KEMPF, G. F.: *J. Exp. Med.*, **73**, 7, 1941.
10. PAGE, I. H., HELMER, O. M., KOHLSTAEDT, K. G., KEMPF, G. F., GAMBILL, W. D., and TAYLOR, R. D.: *Ann. Int. Med.*, **15**, 347, 1941.
11. REMINGTON, J. W., CARTLAND, G. F., DRILL, V. A., and SWINGLE, W. W.: *Am. J. Physiol.*, **140**, 627, 1944.
12. SCHALES, O., STEAD, E. A., JR., and WARREN, J. V.: *Am. J. Med. Sci.*, **204**, 797, 1942.
13. SMITH, C. C., and STEVENS, C. D.: *Ind. Eng. Chem., Anal. Ed.*, **14**, 348, 1942.
14. WAKERLIN, G. E., JOHNSON, C. A., SMITH, E. L., MOSS, W. G., and WEIR, J. R.: *Am. J. Physiol.*, **137**, 515, 1942.

PROGRESS OF MEDICAL SCIENCE SURGERY

UNDER THE CHARGE OF

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A REVIEW OF THE PRESENT CONCEPTS ON FLUID BALANCE

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THE purpose of this paper is briefly to review the present concept of fluid, electrolyte and protein metabolism in the normal and diseased individual, and to emphasize some of the more recent impressions on this subject.

The intake and output of fluid and salt in adults has been well discussed by Peters,⁶⁰ and by Collier and Maddock;¹⁵ it is summarized in Figure 1. Butler and Talbot¹² have more recently reviewed the use of parenteral fluids and have stressed the difference in the daily requirements for infants, adolescents and adults. It can be seen from the numerals in parentheses in this diagram that the output of salt and water can be greatly accelerated in such conditions as vomiting, diarrhea, external fistulas, excessive perspiration, etc. Approximately 8200 cc. of fluid having an electrolyte make-up somewhat similar to plasma are normally excreted into the gastro-intestinal tract per day.³⁰ When the usual daily intake of 2500 cc. is added to this it is apparent that large quantities of fluid pass through the gastro-intestinal tract each 24 hours. If an obstruction or loss of interstitial fluid due

to vomiting, diarrhea or external drainage occurs, the absorption of water and salts is retarded or prevented and it can be readily understood how dehydration may thus occur quite rapidly.

A composite diagram on the available information^{30,60,63,64} of the amount and distribution of body fluid is shown in Table 1. It should be noted that the plasma volume constitutes a relatively small portion of the total body water, but since in the normal individual exchange of fluid in the body tissues occurs quite rapidly,²⁶ the plasma volume is kept at a fairly constant amount.

The movement of fluid is not only rapid and continuous in and out of the gastrointestinal tract and to and from the circulatory system, but also through the other body tissues and the kidney. It is well accepted that approximately 170 liters of water can pass through the glomeruli of a normal individual each day and that about 169 liters of this fluid is reabsorbed.^{25,69} It has also been shown that the colloidal substances of the plasma (albumin, globulin, etc.) leave the vascular system fairly rapidly.^{50,55} Apparently

much of the plasma protein leaving the circulatory system in normal individuals is lost through the liver capillaries, since McCarrell, Thayer and Drinker⁵⁰ found that the concentration of protein in the lymph from the liver is practically identical with that of plasma.

crease there is a reciprocal rise of the other ion. When excessive amounts of sodium are lost,⁶² as might occur in patients with intestinal obstruction or intubation, an external fistula, or diarrhea, the plasma bicarbonate concentration is reduced by an intracellular shift of bicarbonate and

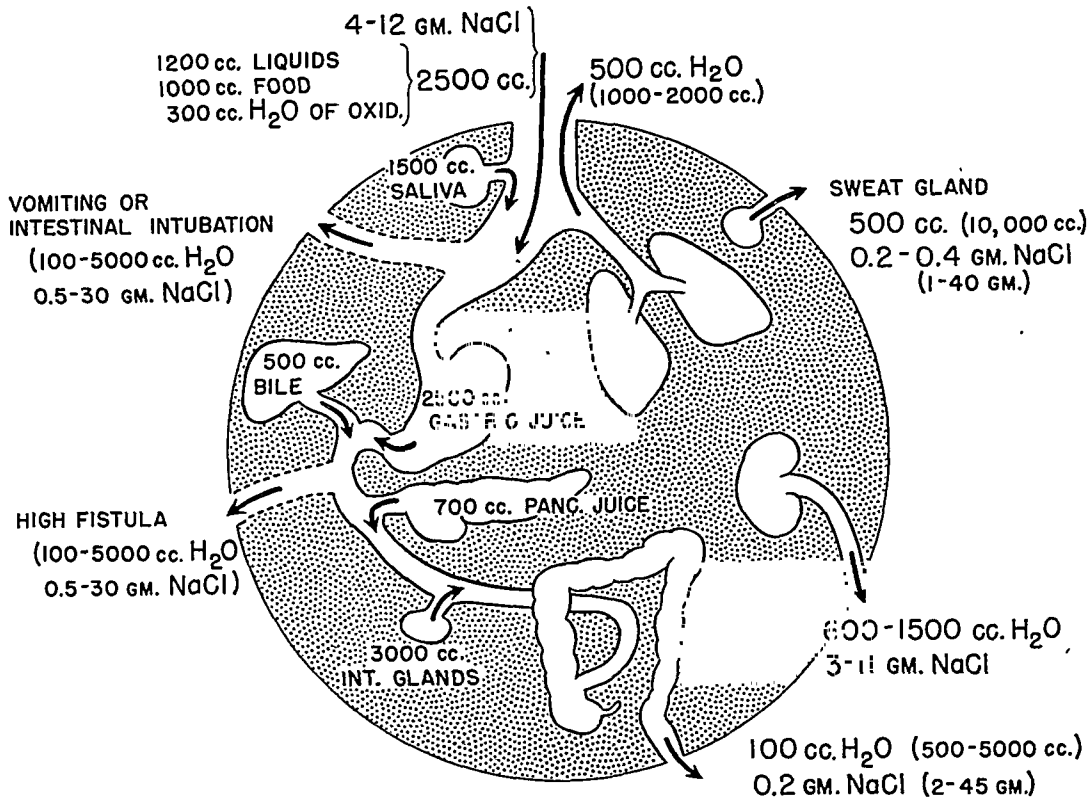


FIG. 1.—The normal and abnormal intake and output of fluid and salt. (The possible abnormal loss of fluid and salt is shown in parenthesis.)

TABLE 1.—THE APPROXIMATE AMOUNT AND DIVISION OF THE BODY FLUID

Normal body fluid compartments	Body weight (%)	154 lb. or 70 kg. man (cc.)
Extracellular:		
Plasma	4-5	3,000
Interstitial	12-18	11,000
Intracellular	40-50	35,000
Total body water, approx.	70	49,000

The importance of sodium and potassium in maintaining a relatively constant amount and distribution of the body fluids has been stressed.^{17,30,31,59,60,64} It has been shown^{30,38,59,60} that the osmotic effect of the anions in the extracellular fluid is not as significant as that of the cations, since when either chloride or bicarbonate de-

the removal of larger amounts of carbon dioxide through the lungs.⁷² If an excess of chloride is present, part of it may pass into the cells or it is eliminated through the kidneys.^{30,60,72} When dehydration is mild, the body gives up water to the kidneys in an attempt to maintain a normal electrolyte pattern; but, as the state

of dehydration becomes more marked, water can no longer be spared in adequate amounts for the formation of urine, so a distortion of the chemical anatomy of the body fluids occurs, usually with a resulting acidosis or alkalosis.^{30,37,59} It is at this stage, when dehydration is fairly marked, that an insufficient amount of water is available to excrete the nitrogenous waste products (prerenal azotemia).^{25,48,59} As a result of this, the non-protein nitrogen or blood urea concentration increases. Marriott⁴⁷ well emphasized the alterations that occur in dehydrated patients and pointed out that if the condition progresses, kidney damage eventually occurs. Very often the urine contains albumin, casts and cells, and after rehydration the kidneys frequently are unable to concentrate urine in a normal fashion. Since the catabolic phase^{32,34,47} is often accelerated when dehydration is present and the kidney function reduced, it may be necessary to force fluids (4000 to 5000 cc. orally or intravenously in the form of 5% dextrose in distilled water with 50 to 100 gm. of amino acids per day) so that the urine volume can be raised sufficiently (2000 to 3000 cc. daily) in order that the kidney may eliminate the accumulated waste products.¹ The giving of adequate sugar and protein seems advisable since the protein stores are being depleted, and the caloric intake derived from dextrose and amino acid solution is usually adequate to stop or to minimize the catabolic process. Amino acid solutions should be given in moderate amounts even though the non-protein nitrogen concentration is elevated, since such cases are usually in a state of negative nitrogen balance.

It has been shown that so far as total body water is concerned, the osmotic effect of the plasma proteins and cell proteins is practically negligible.^{70,73} Thus the state of total body hydration is largely dependent on the presence of sodium and potassium. Starling,⁷⁰ and later Krogh⁴¹ and Landis,^{44,45} demonstrated that the size of the plasma volume in the normal

individual is apparently largely dependent on the amount of plasma protein present. In the diseased state, however, such is usually not the case. In such disorders, when plasma protein is given, it may have only a very transient effect on the blood volume.

In burned patients^{6,27} and animals,^{5,58,68} it has been shown that by giving a physiologic salt solution orally or by injecting it into the burned area,⁸ the tissue tension is apparently increased to a point where the loss of fluid from the circulation is minimized and the absorption of it from the traumatized area is enhanced. From other studies,^{21,24,54} it has been noted that even though the colloid osmotic pressure has been greatly increased, fluid will not be drawn back into the circulation as long as an extracellular depletion of salt and water exists. It has been pointed out repeatedly^{2,41,59,70} that the size of the plasma volume in the normal or diseased patient is not dependent on the protein concentration alone, but is governed by the following factors: (1) the total solute concentration of the extracellular fluid volume and the available water, (2) the osmotic pressure of the interstitial fluid, and (3) the blood filtration pressure minus the tissue tension. It has been demonstrated that the normal exchange of body fluid may be affected because the capillary permeability is increased (due to drugs, inflammation or anoxia)^{40,56,57} or because of endocrine or renal dysfunction (causing a failure of the kidneys to excrete water and salt in a normal fashion).

It was formerly believed that the sodium and potassium ions were largely confined to their specific body fluid compartments. However, more recent studies have shown¹⁸ that under some circumstances such is not the case. Darrow and Engel¹⁸ have demonstrated that in experimental hemorrhagic shock and in anoxia, there is an appreciable intracellular increase in the sodium ion and a decrease in potassium within the liver. Hence, while under certain circumstances osmotic equilibrium between the intracellular and

extracellular phases may occur because of the transfer of electrolytes, this is probably the exception rather than the rule.¹⁶ More commonly, osmotic equality is established following the transfer of water, rather than electrolytes, after alterations in the solute concentration.^{16,30,61} Such changes were demonstrated experimentally by Darrow and Yannet¹⁹ and later confirmed by other workers.^{38,54} Thus, when there is a reduction of the extracellular electrolyte (especially sodium) there is an intracellular shift of fluid and more recently the reverse has been demonstrated⁷⁴ (*i. e.*, when the solute concentration of the extracellular phase is increased there is a shift of fluid from within the cell to the extracellular fluid compartment with a resulting intracellular dehydration). As Gamble³⁰ points out, this exchange of fluid occurs normally in relatively small amounts, but if the shift of fluid is large, the plasma volume may be seriously depleted,^{53,54} or intracellular dehydration may occur with serious consequences.⁷⁷ Decreases in the total extracellular electrolytes and fluid may occur in gastric or intestinal intubation, vomiting, diarrhea, drainage from external fistulas, etc.;^{17,62} increases are usually noted following the giving of large amounts of a physiologic solution of sodium chloride,^{13,74} and in edematous states⁷⁵ (pregnancy, cardiac and renal edema). Peters⁶² clearly demonstrated why patients with an obstruction of the gastro-intestinal tract who are treated by gastric or high intestinal intubation should be denied water and food by mouth while such therapy is being employed. If some oral intake seems desirable, they should be given relatively small amounts of an isotonic salt solution. To permit water or food by mouth, except in some instances of low intestinal intubation, usually accelerates the excretion of gastric, pancreatic and intestinal juices, increases the likelihood of distention and thirst and thus makes the control of the patient from the acid-base and fluid balance standpoint a more difficult one. In fact, it may produce a condition resem-

bling the one that the patient is being treated for.

In considering the methods for giving parenteral fluids it should be recalled that when a solution of 5% dextrose in distilled water is given subcutaneously or intraperitoneally, it causes a temporary extracellular fluid dehydration. It has been shown experimentally^{19,54,79} that sodium and other solutes pass into the area of the injected fluid faster than the glucose and water diffuse out. This temporarily depletes the solutes in the extracellular phase and in order to restore osmotic equality there is an intracellular shift of water. In a patient who is well hydrated, the effect is slight, but when dehydration is present the added decrease of the plasma volume may cause a marked diminution in the blood pressure.

In the above discussion it is emphasized that in certain instances there is an inability on the part of the kidneys to excrete salt and water normally. This may occur in cases of trauma⁹ or burns,^{6,51} infection,^{43,76} anoxia,⁷ cardiac²⁸ or endocrine⁴² disorders, and following anesthesia.^{10,67} This fact should be kept in mind when fluids are being ordered for such cases. The undesirable effects of an excessive saline administration has been stressed,^{3,13,14,15,23,49,71} and of course should be avoided.

Following earlier work on dehydration^{29,30,31} it was felt that the plasma volume was maintained in a relatively constant state at the expense of the interstitial fluid until the patient's condition had become critical. It was believed that the plasma volume decreased only after a marked depletion of the interstitial fluid volume had occurred. However, more recent work has shown^{4,53} that while the interstitial fluid compartment may supply water to the plasma volume, both phases of the extracellular compartment decrease simultaneously during dehydration.

During the past decade many methods and "clinical rules" have been introduced and advocated^{15,20,22,35,39,66,78,80} in the hope

of finding a simple way of controlling the fluid, protein and salt needs. Unfortunately, previous work^{47,52,65} which pointed out the failure of solute concentrations to mirror the state of hydration was largely overlooked, and it has recently again been emphasized that such methods are usually inadequate.^{1,3,4,6,11,13,43} Figure 2 pre-

tained in a patient when a decrease in the total circulating protein is present and a normal or low concentration found in states of overhydration when there is an increase or decrease in the circulating protein, the plasma protein concentration in itself frequently fails to offer any assistance in judging the state of hydra-

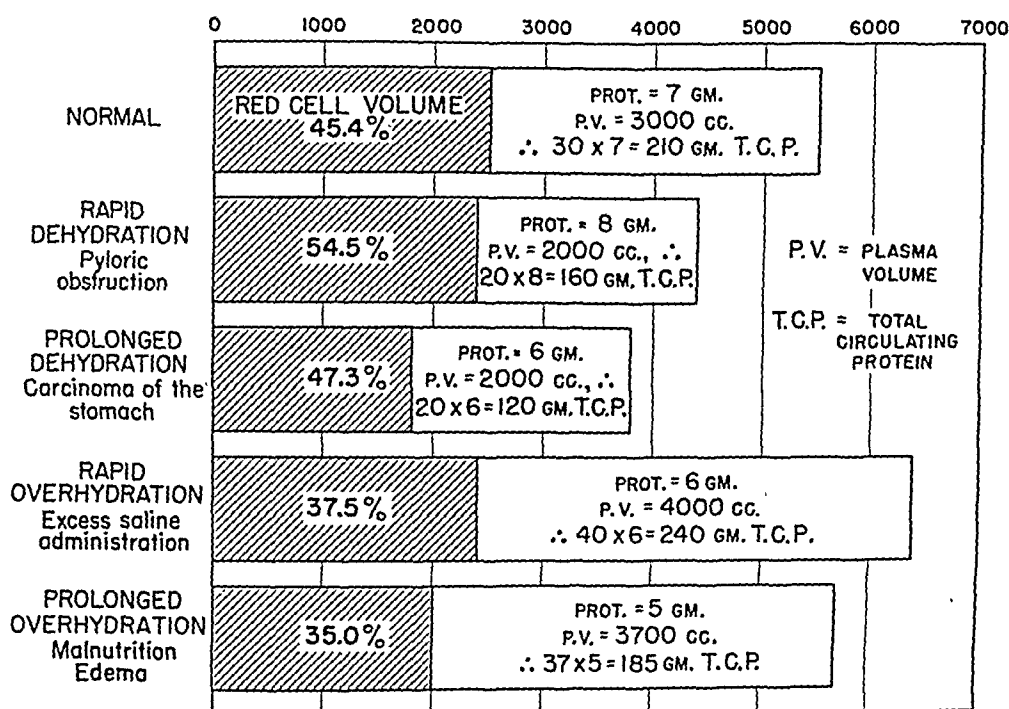


FIG. 2.—The failure of the plasma protein concentration to denote the need for therapy, or the amount of total circulating plasma protein present. (The cross-hatched area equals the red cell mass, and the open area of the bar the extent of the plasma volume.)

TABLE 2.—THE FAILURE OF THE PLASMA CHLORIDE LEVEL TO DENOTE THE TOTAL AMOUNT OF EXTRACELLULAR CHLORIDE

Type of case	Plasma chloride (conc. meq./L.)	Extracellular fluid (cc.)	Total meq. of chloride in the extracellular fluid
Normal	105	14,000	1470
Pancreatic, biliary or high intestinal fistula	118	10,000	1180
Pyloric obstruction	88	10,000	880
Malnutrition, burn, and cardiac edema	88	20,000	1760

sents in a simplified form the impressions gained recently and demonstrates how the cell volume and protein concentration may be misleading. The upper column in Figure 2 represents the normal findings and the lower columns show the changes that may occur in dehydration and overhydration. Since a high, normal, or low plasma protein concentration may be ob-

tion or nutrition. Because of the fairly wide deviation of the normal cell volume,³³ and the withdrawal or destruction of cells in shock³⁵ and dehydration⁴⁷ the hematocrit may also be misleading.

Table 2 demonstrates the fallacy of employing the plasma chloride level. These figures are theoretical but are based on the findings taken from experimental

and clinical studies.^{1,4,52} It should be noted that high, normal or low values may occur in dehydration and that excessive amounts of extracellular fluid chloride may be present when normal or low concentrations exist.

Figure 3 demonstrates some of the more common changes in the blood chemical concentrations that may occur. Such studies may aid greatly in determining

a decrease in the solute concentration (Fig. 4, marked dehydration) may take place when a state of dehydration exists. A decrease in the solute concentrations, while not shown in Figure 4, can also occur in states of overhydration.

Thus, it becomes important to think in terms of total body water and salt rather than solute concentrations alone, since changes in the volume and concentration

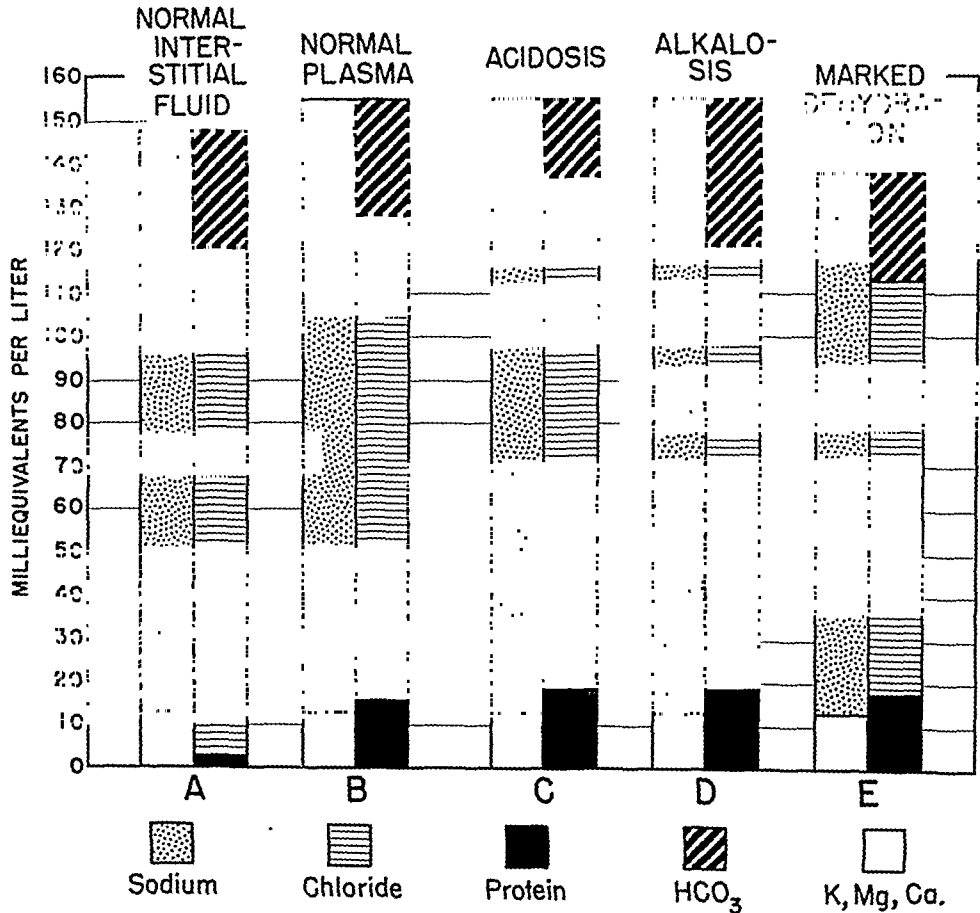


FIG. 3.—The composition of the normal extracellular fluid (A and B) and the possible structural changes that may occur in the plasma during disease (C, D, E).

the acid-base balance, but in themselves do not permit quantitative conclusions to be drawn on the state of hydration. Figure 4 was included in order to help in visualizing the alterations in concentration and volume that might occur in such cases. It can be seen that an increase or a decrease in the total amount of water or salt may occur with little change in concentration, and it is also evident that

can occur in numerous different ways. Elaborate studies to determine the state of fluid balance often are of little value since the control volume cannot be estimated accurately³³ and the state of hydration can be determined fairly well from a careful history and physical examination. Changes in hydration can usually be demonstrated in the course of a physical examination (eyeball tension, condition of

tongue, elasticity of the skin, etc.) and an estimate of the severity of the disorder may be made by a careful history (type, severity and duration of illness), and by observations of the response of the patient to therapy (changes in the amount and in the specific gravity of urine, in the turgor of the skin, in mental alertness, and in the weight and thirst of the individual in question).

The importance of these obvious and easily discernible findings ought not be

underestimated in the evaluation and treatment of dehydration or overhydration. Often too much reliance is placed on single or even repeated isolated determinations of concentration of substances in the blood, especially chloride and protein. To be of value such data must be considered in relation to the general state of nutrition and hydration of the patient as indicated by the history, the physical examination, and the volume and specific gravity of the urine.

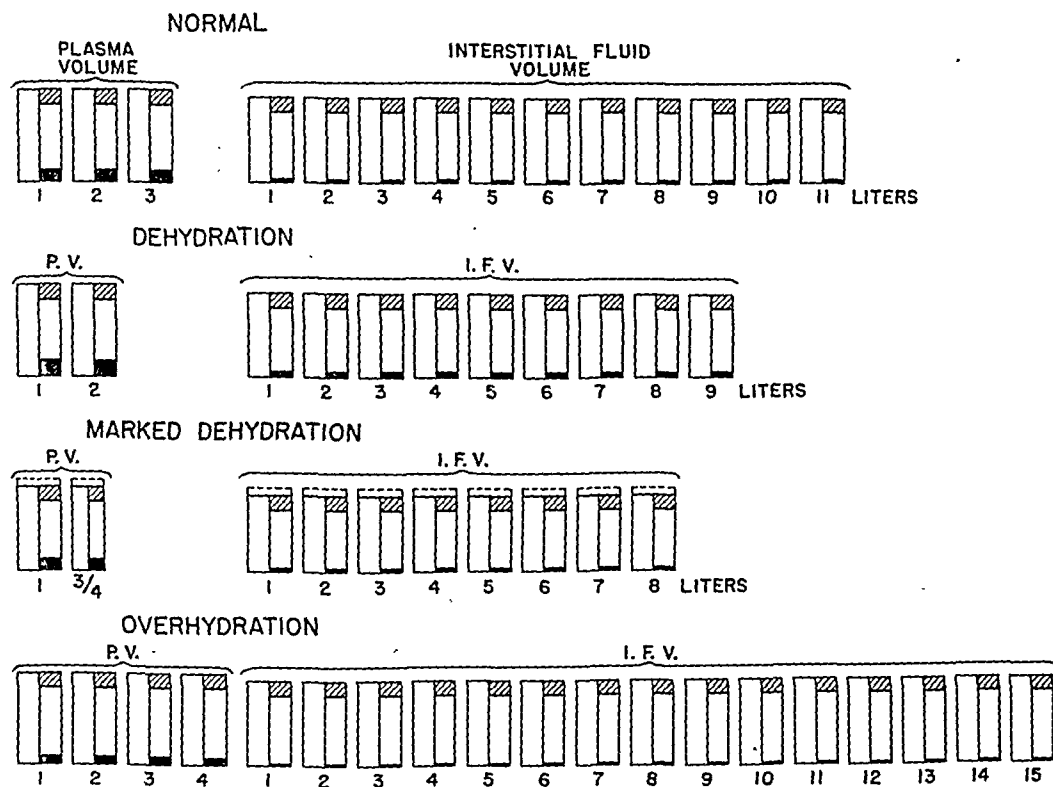


FIG. 4.—Changes in the extracellular fluid volume (concentration changes may occur as shown in Figure 3 but also volume alteration should be taken into consideration).

REFERENCES

- (1.) Abbott, W. E.: Chemical Alterations in Surgical Patients (to be published).
- (2.) Abbott, W. E., Hirshfeld, J. W., and Meyer, F. L.: *Surg., Gynec. and Obst.*, 81, 25, 1945.
- (3.) Abbott, W. E., and Mellors, R. C.: *Arch. Surg.*, 46, 277, 1943.
- (4.) Abbott, W. E., Mellors, R. C., and Muntwyler, E.: *Ann. Surg.*, 117, 39, 1943.
- (5.) Abbott, W. E., Meyer, F. L., Hirshfeld, J. W., and Griffin, G. E.: *Surgery*, 17, 794, 1945.
- (6.) Abbott, W. E., Pilling, M. A., Griffin, G. E., Hirshfeld, J. W., and Meyer, F. L.: *Ann. Surg.*, 122, 678, 1945.
- (7.) Adolph, E. F.: *Am. J. Physiol.*, 111, 75, 1935.
- (8.) Berman, J. K., Peterson, L., and Butler, J.: *Surg., Gynec. and Obst.*, 78, 337, 1944.
- (9.) Browne, J. S. L., Karady, S., and Selye, J.: *J. Physiol.*, 97, 1, 1939.
- (10.) Bruger, M., Bourne, W., and Dreyer, N. B.: *Am. J. Surg.*, 9, 82, 1930.
- (11.) Butler, A. M.: *New England J. Med.*, 220, 827, 1937.
- (12.) Butler, A. M., and Talbot, N. B.: *New England J. Med.*, 231, 585, 1944.
- (13.) Collier, F. A., Campbell, K. N., Vaughan, H. H., Iob, L. V., and Moyer, C. A.: *Ann. Surg.*, 119, 533, 1944.
- (14.) Collier, F. A., Iob, V., Vaughan, H. H., Kalder, N. B., and Moyer, C. A.: *Ann. Surg.*, 122, 663, 1945.
- (15.) Collier, F. A., and Maddock, W. G.: *Surg., Gynec. and Obst.*, 70, 340, 1940

- (16.) Darrow, D. C.: *Ann. Rev. Physiol.*, 6, 95, 1944. (17.) Darrow, D. C.: *New England J. Med.*, 233, 91, 1945. (18.) Darrow, D. C., and Engel, F. L.: *Am. J. Physiol.*, 145, 32, 1945. (19.) Darrow, D. C., and Yannet, H.: *J. Clin. Invest.*, 14, 266, 1935. (20.) Drew, C. R., Scudder, J., and Papps, J.: *Surg., Gynec. and Obst.*, 70, 859, 1940. (21.) Dunphy, J. E., and Gibson, J. G., 2nd: *Surgery*, 14, 509, 1943.
- (22.) Elman, R.: *Bull. New York Acad. Med.*, 20, 220, 1944. (23.) Evans, G. H.: *J. Am. Med. Assn.*, 57, 2126, 1911.
- (24.) Fine, J., Frank, H. A., and Seligman, A. M.: *J. Clin. Invest.*, 23, 731, 1944. (25.) Fishberg, A. M.: *Hypertension and Nephritis*, 4th ed., Phila., Lea & Febiger, 1939. (26.) Flexner, L. B., Gellhorn, A., and Merrell, M.: *J. Biol. Chem.*, 144, 35, 1942. (27.) Fox, C. L., Jr.: *J. Am. Med. Assn.*, 124, 207, 1944. (28.) Futcher, P. H., and Schroeder, H. A.: *Am. J. Med. Sci.*, 204, 52, 1942.
- (29.) Gamble, J. L.: *Bull. Johns Hopkins Hosp.*, 61, 151, 1937. (30.) Gamble, J. L.: *Chemical Anatomy, Physiology and Pathology of Extracellular Fluid, A Lecture Syllabus*, Boston, Spaulding-Moss, 1941. (31.) Gamble, J. L., and McIver, M. A.: *J. Exp. Med.*, 48, 859, 1928. (32.) Gamori, P., and Podhradsky, L.: *Acta med. Scand.*, 92, 515, 1937. (33.) Griffin, G. E., Abbott, W. E., Pride, M. P., Muntwyler, E., Mautz, F. R., and Griffith, L.: *Ann. Surg.*, 121, 352, 1945.
- (34.) Haden, R. L., and Orr, T. G.: *Bull. Johns Hopkins Hosp.*, 34, 26, 1923. (35.) Harkins, H. N.: *Arch. Path.*, 38, 147, 1944. (36.) Harkins, H. N., Cope, O., Evans, E. I., Phillips, R. A., and Richards, D. W., Jr.: *J. Am. Med. Assn.*, 128, 475, 1945. (37.) Hartmann, A. F.: *Am. J. Dis. Child.*, 35, 557, 1928. (38.) Hastings, A. B., and Eichelberger, L.: *J. Biol. Chem.*, 117, 73, 1937.
- (39.) Jenkins, H. P., Schafer, P. W., and Owens, F. M., Jr.: *Arch. Surg.*, 47, 1, 1943. (40.) Jones, C. M., Eaton, F. B., and White, J. C.: *Arch. Int. Med.*, 53, 649, 1934.
- (41.) Krogh, A.: *Anatomy and Physiology of the Capillaries*, 2nd ed., New Haven, Yale Univ. Press, 1929.
- (42.) Loeb, R. F.: *New York Acad. Med. Bull.*, 18, 263, 1942. (43.) Lyons, C.: *J. Am. Med. Assn.*, 123, 1007, 1943. (44.) Landis, E. M.: *Physiol. Rev.*, 14, 404, 1934. (45.) Landis, E. M.: *Am. J. Med. Sci.*, 193, 297, 1937. (46.) Lanson, H. D., Bradley, S. E., and Cournand, A.: *J. Clin. Invest.*, 23, 381, 1944.
- (47.) Marriott, W. McK.: *Physiol. Rev.*, 3, 275, 1923. (48.) Marriott, W. McK., Hartmann, A. F., and Senn, J. E.: *J. Pediatr.*, 3, 181, 1933. (49.) Matas, R.: *Ann. Surg.*, 79, 643, 1924. (50.) McCarrell, J. D., Thayer, S., and Drinker, C. K.: *Am. J. Physiol.*, 113, 79, 1941. (51.) McIver, M. A.: *Ann. Surg.*, 97, 670, 1933. (52.) McIver, M. A., and Gamble, J. L.: *J. Am. Med. Assn.*, 91, 1589, 1928. (53.) Mellors, R. C., Muntwyler, E., Mautz, F. R., and Abbott, W. E.: *J. Biol. Chem.*, 144, 785, 1942. (54.) Mellors, R. C., Muntwyler, E., and Mautz, F. R.: *J. Biol. Chem.*, 144, 773, 1942. (55.) Metcalf, W.: *J. Clin. Invest.*, 23, 403, 1944. (56.) Moon, V. H.: *Ann. Int. Med.*, 8, 1633, 1935. (57.) Moon, V. H.: *Am. J. Clin. Path.*, 11, 361, 1941. (58.) Moyer, C. A., Collier, F. A., Iob, V., Vaughan, H. H., and Marty, D.: *Ann. Surg.*, 120, 367, 1944. (59.) Muntwyler, E., and Mautz, F. R.: *Med. Physics*, p. 371, 1944.
- (60.) Peters, J. P.: *Body Water: The Exchange of Fluids in Man*, Baltimore, Thomas, 1935. (61.) Peters, J. P.: *Harvey Lectures*, 33, 112, 1937-38. (62.) Peters, J. P.: *Univ. Pennsylvania Bicentennial Conference*, Phila., Univ. Penna. Press, 1941. (63.) Peters, J. P.: *Ann. Rev. Physiol.*, 4, 89, 1942. (64.) Peters, J. P.: *Physiol. Rev.*, 24, 491, 1944. (65.) Peters, J. P., Wakeman, A. M., and Eisenman, A. J.: *J. Clin. Invest.*, 3, 491, 1927. (66.) Power, F. H., Pedersen, S., and Maddock, W. G.: *Surgery*, 12, 438, 1942. (67.) Pringle, H., Maunsell, R. C. B., and Pringle, S.: *Brit. Med. J.*, 2, 542, 1905.
- (68.) Rosenthal, S. M.: *Pub. Health Rep.*, 58, 513, 1943.
- (69.) Smith, H. W.: *The Physiology of the Kidney*, New York, Oxford Univ. Press, 1937. (70.) Starling, E. H.: *J. Physiol.*, 19, 312, 1895-96.
- (71.) Trout, H. H.: *Surg., Gynec. and Obst.*, 16, 560, 1913.
- (72.) Van Slyke, D. D.: *Symposia on Quantitative Biology*, 1, 184, 1933. (73.) Van Slyke, D. D., Wu, H., and McLean, F. C.: *J. Biol. Chem.*, 56, 765, 1923.
- (74.) Warren, J. V., Merrell, A. J., and Stead, E. A., Jr.: *J. Clin. Invest.*, 22, 635, 1943. (75.) Warren, J. V., and Stead, E. A., Jr.: *Arch. Int. Med.*, 73, 138, 1944. (76.) Wilder, T. S., and Drake, T. G. H.: *J. Clin. Invest.*, 7, 353, 1929. (77.) Winkler, A. W., Elkinton, J. R., Hopper, J., and Hoff, H. E.: *J. Clin. Invest.*, 23, 103, 1944. (78.) Wolff, W. A., and Lee, W. E.: *Ann. Surg.*, 115, 1125, 1942.
- (79.) Yannet, H., and Darrow, D. C.: *J. Biol. Chem.*, 134, 721, 1940.
- (80.) Zintel, H. A.: *Am. J. Med. Sci.*, 207, 253, 1944.

OPHTHALMOLOGY

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RETINAL LESIONS IN ACUTE DISSEMINATE LUPUS ERYTHEMATOSUS

By H. P. WAGENER, M.D.

IN many cases of "fever of undetermined origin," before the clinical syndrome is sufficiently well developed to permit a definite diagnosis, ophthalmoscopic examination of the ocular fundus is made in the hope of finding in the optic disk, the retina, or the choroid some clue to the nature of the systemic disease. In a few of the diseases which might fall into this category, such as subacute bacterial endocarditis and miliary tuberculosis, the ophthalmoscopically visible lesions are recognized to be sufficiently characteristic to warrant a fairly accurate diagnosis. In others, such as disseminate lupus erythematosus, Libman-Sachs disease, and periarteritis nodosa, however, no definitely diagnostic fundus lesions have been described as yet. Among patients with acute disseminate lupus erythematosus, lesions in the retina occur rather frequently. It seems possible that, from more universal studies of the retina in these cases with more accurate descriptions of the nature and course of the lesions, a reasonably characteristic and diagnostic ophthalmoscopic picture might evolve.

Unfortunately, much of the available data on the retinal lesions in this disease is to be found only in rather brief notes of fundus examinations in reports of individual cases. Some of these notes are rather vague. Thus Guion and Adams⁷ state that in 1 of their patients "retinitis" had been observed by a previous examiner. Another of their patients had "postneurotic optic atrophy." Only a few reports of histologic studies of the eyes have been

presented. Yet, among the case reports, there can be found descriptions of retinal lesions characteristic of, or associated with, the toxic, inflammatory, vascular, and embolic features of the systemic disease.

In 1935, Pillat¹⁶ reported his ophthalmoscopic observations in 48 cases of chronic lupus erythematosus. In 16 cases, he found isolated lesions in the choroid which resembled healed tuberculous choroiditis. In 3 of these patients there was an acute exacerbation of the lupus. In 2 of the 3, Pillat found additional foci of acute choroiditis which he believed were characteristically tuberculous. He presented his observations as evidence in favor of the tuberculous etiology of lupus erythematosus. Keil⁸ expressed the opinion that the lesions described by Pillat might well be tubercles in the choroid but that they were most probably incidental findings and not a manifestation of systemic lupus. Previous to this, in 1929, Bergmeister³ had described lesions which he interpreted as metastatic tubercles in the retina in a patient with acute disseminate lupus erythematosus in whom necropsy revealed disseminated tuberculosis. In the right eye, the disk was hyperemic and there were irregular white patches along the retinal veins. In the left eye, there were many "cotton wool" exudates and there were a number of small white dots in the macula. The eyes were not examined histologically.

Undoubtedly, the lesions described by Bergmeister are those seen most commonly in cases of acute disseminate lupus

erythematosus. However, as has been demonstrated by the histologic studies of Maumenee,¹⁵ Bergmeister misinterpreted their nature. In 1922, Keith and Rowntree⁹ reported on their studies of the renal complications in 4 cases of this disease. In one of their patients the fundi were normal at the initial examination. However, 1 month before the patient's death, 2 cotton wool patches were observed in the retina. During the following 2 weeks, more of these patches developed; so that, at the last examination, 12 were present in the right retina and 6 in the left. In the main, these cotton wool patches tend to develop in the terminal phases of the disease. However, they are not necessarily a fatal prognostic sign, since they may appear during an acute exacerbation from which the patient may recover, at least temporarily. In 1935, Baehr, Klemperer, and Schiffrin² reported their findings in 23 cases of acute disseminate lupus. They stated that lesions were present in the ocular fundi of 12. They mentioned the presence of fluffy exudates but they called attention also to perivascular hemorrhages and they noted circumpapillary edema in 2 cases. In the discussion of their paper, Longcope¹⁴ stated that he had observed in 1 case marked swelling of the optic disk during an acute exacerbation of the eruption and, in another, swelling of the disk, hemorrhages and small exudates which disappeared coincident with temporary disappearance of the rash and subsidence of the fever.

Kurz,¹² in 1938, was probably the first to demonstrate the true histology of these white patches in the retina. In a case which he observed 1 month before death, he noted 4 or 5 white patches, varying in size from $\frac{1}{4}$ to $\frac{1}{2}$ disk diameter, in the macular retina superficial to the retinal vessels. The disks were normal. A few small hemorrhages were present in the retina. Histologic examination of the eyes obtained at necropsy demonstrated that the white patches consisted of varicose hypertrophy or ganglioform degeneration of nerve fibers (cytoid bodies). Kurz

thought the lesions in his case were identical with the retinitis septica of Roth and considered them to be of toxic and not bacterial embolic origin. He made no mention of lesions in the retinal vessels.

Essentially similar ophthalmoscopic findings have been reported by Rose and Pillsbury,¹⁷ Keil,⁸ Maumenee,¹⁵ Stickney and Keith,¹⁹ and Cluxton and Krause.⁴ It would be difficult to say whether the small light spots described by Abramowicz and Dulewicz¹ represented edema residues or were actually only hyaline deposits in the lamina vitrea of the choroid. Hemorrhages and exudates were present in the retinas of 3 of the 4 cases reported by Cluxton and Krause.⁴ The optic disks were normal. The authors did not advance any definite theory as to the origin of these lesions. They said: "The lesions are not necessarily associated with renal disease because the blood pressure is usually normal, nor are they related to bacterial embolic phenomena because the blood cultures are for the most part sterile." "The evidence points to the lesions being local in origin and representing but one of the manifestations of a systemic disease." Rose and Pillsbury¹⁷ stated that intraocular lesions were common and included papilledema, sometimes with extension of the edema into and beneath the retina, retinal detachment and atrophy, guttate retinitis, perivascular exudates and hemorrhages, and choroidal degeneration. They expressed the opinion that these lesions were a part of the widespread vascular disease. The vascular lesions as described by Baehr, Klemperer and Schiffrin² include: (1) capillary dilatation with extravasation of blood and serum; (2) proliferative endothelial vascular lesions with thrombus formation; and (3) degenerative or necrotizing lesions in the walls of capillaries, arterioles and venules, often with hemorrhages into adjacent tissues.

Keil⁸ also thought that the lesions in the retina were of vascular origin. He stated: "In systemic lupus erythematosus, the fundi often reveal alterations. The

evidence appears to indicate that these changes arise primarily in relation to the blood vessels." He observed that the hemorrhages and the soft fluffy exudates were arranged in general in perivascular fashion and he thought that the exudates were probably simply collections of edematous fluid similar to that in the upper part of the corium skin. He did not regard the lesions as pathognomonic of lupus erythematosus and was not able to correlate them precisely with the severity of the clinical course of the disease though he did regard them as definite evidence that the disease had become systemic. Keil called attention to his personal observations of peripapillary edema of varying severity and expressed the opinion that this lesion occurred more commonly than was generally suspected. He thought that this transudation of edema fluid into the peripapillary retina was the result of vascular damage in the retina and was not due to an increase in intracranial pressure. Baehr, Klemperer and Schiffrin² also expressed the opinion that the lesions in the retina were not due to hypertension but were analogous probably to the lesions observed on the fingers, primary vascular alterations with hemorrhagic extravasations and perivascular exudation. The involved skin around the nail bed of the fingers was seen to contain many more patent and dilated capillaries than normal with extravasation of serum and red cells into the subcutaneous tissues. Stokes, Beerman and Ingraham²⁰ state: "As the discoid type of lesion is expressive of local cutaneous infection-allergy of the follicular inflammatory type with atrophy, so the acute disseminate type is the clinical type of lupus erythematosus with multiform disseminated cutaneous and systemic lesions resulting from allergic inflammation of the vascular system." "The vasculo-allergic type of 'lupus erythematosus' then, may be preponderantly local and cutaneous in its manifestations, or preponderantly systemic—fever, lymphadenopathy; leukopenia, absolute or relative, with or without thrombocytopenia, and

with demonstrable vascular lesions of the eyes, kidney and endocardium."

The theory that this type of retinopathy is of vascular origin lacks histologic support. In 1940, Maumenee¹⁵ reported the results of ophthalmoscopic and histologic studies of the eyes of 4 patients with acute disseminate lupus erythematosus and of 1 patient with chronic disseminate lupus erythematosus. In his opinion, the lesions found were to be regarded as a manifestation of generalized toxemia. He described the following 3 typical lesions: (1) Small, fluffy, yellowish white to white spots located in the superficial layers of the retina, never larger than the disk, usually in the posterior part of the fundus, and very similar in appearance to the cotton wool patches of hypertensive retinopathy. These patches were present in all cases. Histologically they were shown to be areas of cytooid bodies. (2) Small hemorrhages placed superficially in the retina and not located in relation to the white patches nor to the larger retinal vessels. These were observed ophthalmoscopically in 3 cases and were found microscopically in the nerve fiber layer of the retina. (3) Slight papilledema. This was observed ophthalmoscopically in 3 cases and was confirmed histologically in 2. In 1 case, there was noted ophthalmoscopically slight generalized blurring of the choroidal reflex which was thought to indicate subretinal edema. Histologic examination in this case revealed serous exudation and hemorrhages in the stroma of the choroid in an area of about 2 or 3 disk diameters around the optic nerve. The choroidal vessels showed moderate hyaline degeneration of the intima and proliferation of the adventitia. In this same case there was slight hyaline degeneration of the intima of the retinal arterioles typical of arteriolar sclerosis. The blood pressure was 140/90. In the other 4 cases the vessels were normal.

In addition to the above findings, Maumenee noted histologically in all the cases a slight round cell infiltration of the choroid similar to the "septic choroiditis"

described by Friedenwald and Rones.⁵ This was not detected ophthalmoscopically. Ophthalmoscopically visible lesions of apparently similar histologic type were described by Semon and Wolff¹⁸ in a case of acute disseminate lupus erythematosus. They observed in each fundus round white elevated lesions resembling tubercles of the choroid. One of these was located underneath a retinal vein. Histologic examination revealed a fairly generalized invasion of the choroid with inflammatory cells. At the site of one of the ophthalmoscopically observed lesions there was well-marked subretinal exudate containing inflammatory cells (lymphocytes, a few neutrophils and a few large mononuclears), some pigment, some spindle cells, and capillary vessels (granulation tissue). There was no evidence of tuberculosis. The retina was normal. Lesions of this type may be considered possibly as manifestations of the chronic infections, frequently streptococcic, which may be a factor in the etiology of the disease.

In my experience, the type of toxic retinopathy described by Maumenee¹⁵ is the type of lesion encountered most frequently in patients with acute disseminate lupus erythematosus. Instances of gross organic involvement of the retinal vessels are much less common. Klauder and Ellis¹⁰ described in 1 patient various sized, irregular, fluffy, cloud-like patches and a few small hemorrhages scattered through the retinas particularly around the disks. This description would suggest the ordinary type of toxic retinopathy. However, the patient improved under treatment with gold sodium thiosulphate and, 1 year and 3 months after the original observation, the "exudative retinitis" had disappeared. There was slight pallor of the disks. Some of the larger retinal vessels were "replaced by scar tissue" and the other vessels showed varying degrees of sclerosis and a corkscrew appearance. There was collateral circulation on the disks. The vision which had been 3/60 originally was now 6/60. In the discussion of this case, Lillie interpreted the lesions as diffuse peri-

vasculitis and periphlebitis associated with pallor of the disks and the formation of new blood vessels on and around the disks.

Goldstein and Wexler⁶ described bilateral secondary optic atrophy (post-neuritic) in a fatal case which was diagnosed clinically as acute disseminate lupus but in which necropsy did not reveal confirmatory evidence of this disease. Ophthalmoscopically, both optic disks were pearly white with serrated edges. The retinal arteries and veins were extremely narrow. There was some periarterial sheathing. Scattered throughout the posterior parts of the fundi were numerous discrete punched-out areas of retinal atrophy bordered by a fringe of pigment, always located in relation to a retinal vessel. Histologic examination revealed atrophy and gliosis of the optic nerves with the preservation, however, of many normal blood vessels. There was atrophy of the walls of the larger arterioles in the retina with constriction of the lumen and degeneration of the media which was replaced by almost acellular fibrillar or homogeneous material staining faintly with eosin and resembling hyaline. In some places there was present in addition a perivascular fibrosis so extensive as to produce discrete areas of atrophy of the retina with compact fibrous tissue replacement. The choroid was not involved.

At a recent meeting of the American Ophthalmological Society, Koch and McGuire¹¹ described somewhat similar findings in a case diagnosed clinically as acute disseminate lupus erythematosus. Necropsy was not obtained. Ophthalmoscopic examination revealed periarteritis and periphlebitis with hemorrhage and exudation into the retina. The lesions gradually became more extensive with involvement of more vessels. Subsequently some of the vessel branches were apparently fibrosed and obliterated and pallor of the optic disks developed.

In view of the rather frequent occurrence of vegetative endocarditis in cases of acute disseminate lupus erythematosus, it is rather surprising that embolic phe-

nomena are not observed more often in the retina. Keil⁸ mentions that he had seen a case with blindness (in 1 eye?) which was attributed to an "embolism" of the central artery of the retina with secondary glaucoma. Keil was inclined to blame the occurrence of the embolism on an injection of gold. Recently I had the opportunity of observing a young girl in whom the clinical diagnosis of acute

disseminate lupus erythematosus was confirmed at necropsy. Vegetations were found on the heart valves (non-bacterial). About a month before her death, there was an area of ischemic edema in 1 retina associated with closure, probably embolic, of a small terminal arteriole. A few days before her death, a number of petechial hemorrhages with white centers were present in each retina.

REFERENCES

- (1.) Abramowicz, I., and Dulewicz, M.: *Ann. d'Ocul.*, 170, 599, 1933. (2.) Baehr, G., Klemperer, P., and Schiffrin, A.: *Trans. Assn. Am. Phys.*, 50, 139, 1935. (3.) Bergmeister, R.: *Wien. Med. Wchnschr.*, 79, 1116, 1929. (4.) Cluxton, H. E., Jr., and Krause, L. A. M.: *Ann. Int. Med.*, 19, 843, 1943. (5.) Friedenwald, J. S., and Rones, B.: *Arch. Ophth.*, 5, 175, 1931. (6.) Goldstein, I., and Wexler, D.: *Arch. Ophth.*, 8, 852, 1932. (7.) Guion, C. M., and Adams, E. C.: *Am. J. Med. Sci.*, 205, 33, 1943. (8.) Keil, H.: *Arch. Int. Med.*, 66, 339, 1940. (9.) Keith, N. M., and Rowntree, L. G.: *Trans. Assn. Am. Phys.*, 37, 487, 1922. (10.) Klauder, J. V., and Ellis, V. M.: *Arch. Ophth.*, 21, 893, 1939. (11.) Koch, F. L. P., and McGuire, W. P.: *Trans. Am. Ophth. Soc.*, 1945 (in press). (12.) Kurz, O.: *Ztschr. f. Augenh.*, 95, 315, 1938. (13.) Lillie, W. I.: Discussion of paper of Klauder and Ellis. (14.) Longcope, W. T.: Discussion of paper of Baehr, Klemperer, and Schiffrin. (15.) Maumenee, A. E.: *Am. J. Ophth.*, 23, 971, 1940. (16.) Pillat, A.: *Arch. f. Ophth.*, 133, 566, 1935. (17.) Rose, E., and Pillsbury, D. M.: *Ann. Int. Med.*, 12, 951, 1939. (18.) Semon, H. C., and Wolff, E.: *Proc. Roy. Soc. Med.*, 27, 153, 1933. (19.) Stickney, J. M., and Keith, N. M.: *Arch. Int. Med.*, 66, 643, 1940. (20.) Stokes, J. H., Beerman, H., and Ingraham, N. R.: *Am. J. Med. Sci.*, 207, 540, 1944.

PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF DECEMBER 18, 1945

The Effect of the Alkyl Sulfates on Gastric Secretion in the Rat. H. SHAY, M.D., S. A. KOMAROV, M.D., PH.D., H. SIPLET, B.S., and M. GRUENSTEIN (Medical Research Laboratory, Samuel S. Fels Fund). Adequately starved Wistar-strain white rats grown in our own colony were anesthetized with ether and intracecal urethane. The pylorus was tied, avoiding damage to any blood vessels. The esophagus was exposed in the neck and a loose ligature was placed around it. The stomach was then lavaged through a stomach catheter with 4 cc. of warm normal saline. The stomach was emptied completely and 2 cc. of the test solution was introduced. The esophageal ligature was tied as the stomach catheter was removed. The esophagus was cut proximal to the ligature and its proximal end was sutured to the skin by a submucous suture. The abdominal and neck incisions were then closed. Half of the animals in each group received atropine (25 mg. per 100 gm.) subcutaneously as the operation was started.

They recovered rapidly from their anesthesia. Six hours after the gastric instillation of the test solution they were sacrificed and the gastric contents collected, measured and analyzed for pH, free and total acid, chlorides, pepsin and mucin.

The test solutions included distilled water, 0.1%, 0.5% and 2% solutions of a very pure sodium dodecyl sulfate dissolved in distilled water. In the 8 groups of 8 to 11 animals each, the results within each group were sufficiently uniform to justify the following conclusions:

Resorption may occur in the rat's stomach. This capacity was especially evident in the atropinized group in which the mean rate of absorption following the

instillation of distilled water was 0.13 cc. per hour per 100 gm. body weight.

When sodium dodecyl sulfate was in contact with the gastric mucosa it exerted a stimulating effect upon the gastric secretory mechanism, the nature of which was related to the concentration of the solution. With 0.1% and 0.5% solutions all secretory elements—the parietal, peptic and mucus secreting cells—are strongly stimulated. The 2% solution exerts a selective effect in that only the mucus secreting cells are stimulated. The stimulating effect of the sodium dodecyl sulfate becomes progressively stronger with the increase in concentration from 0.1% to 2%. From a comparison of the results in the atropinized and non-atropinized animal, it becomes clear that stimulation of the parietal and peptic cells by the weak solutions is entirely a reflex effect through the vagus, while the stimulation of the mucus secreting cells in all concentrations was a twofold action—partly reflex through the vagus and in part a direct action upon the mucus secreting cells.

A Study of the Influence of Various Dietary Deficiencies on the Response of Mice to the Virus of Poliomyelitis. J. H. JONES, PH.D., C. FOSTER and W. HENLE, M.D. (Depts. of Physiol. Chem. and Pediatrics, Univ. of Penna. and Children's Hosp.). In a previous report¹ it was shown that either a dietary deficiency of vitamin B₁ or partial starvation of animals on a complete diet increased the resistance of mice to the murine adapted strain of poliomyelitis virus. Similar observations have been made by Rasmussen *et al.*² By use of the paired feeding technique it was subsequently demonstrated³ that the vitamin deficiency exhibited a greater protection than did the

restriction of food intake, indicating that the effect of the vitamin deficiency could not be entirely due to the inanition.

Following these observations the effect of several other deficiencies on the response of mice to the virus of poliomyelitis has been studied. These deficiencies have included that of the B₂ complex, B₆, protein, and tryptophane. In each case the animals were continued on the deficient diet until fairly marked deficiency symptoms were manifest. They were then inoculated intracerebrally with an amount of virus that would produce paralysis and death in about 80% of the animals on a complete diet. In the case of each of the above deficiencies total deaths were 80% or more within 28 days after inoculation when the experiments were discontinued. The incidence of paralysis varied from above 50% to above 80%. Some of the deaths were due to the deficiencies as indicated by numerous deaths in corresponding groups on deficient diets but injected with a suspension of uninfected brain. There was no conclusive evidence that any of the above deficiencies (vitamin B₂ complex, vitamin B₆, protein or tryptophane) either increased or decreased the resistance of mice to the virus of poliomyelitis.

1. FOSTER, C., JONES, J. H., HENLE, W., and DORFMAN, F.: *J. Exp. Med.*, **79**, 221, 1944.

2. RASMUSSEN, A. F., JR., WAISMAN, H. A., ELVEHJEM, C. A., and CLARK, P. F.: *J. Infect. Dis.*, **74**, 41, 1944.

3. FOSTER, C., JONES, J. H., HENLE, W., and DORFMAN, F.: *J. Exp. Med.*, **80**, 257, 1944.

Observations on an Oligodynamic Action of Copper on Human Erythrocytes. M. H. JACOBS, PH.D., and D. R. STEWART, PH.D. (Dept. of Physiology, Univ. of Penna.). The striking effect of traces of copper in decreasing the permeability of human erythrocytes to glycerol reported by Jacobs and Corson in 1934 has been studied more quantitatively by improved methods. It has been found that in a 0.3 M solution of glycerol lightly buffered at pH 6.5, an easily detectable copper effect may be produced by a concentra-

tion of copper chloride of 8×10^{-8} M and a 90% decrease of permeability to glycerol by one of 6.4×10^{-7} M. Several lines of evidence indicate that the copper effect, which is readily reversible, is confined to the surface of the cell. Calculation shows that under the conditions of these experiments, at the higher of the 2 concentrations mentioned, there might be available for combination with each cell a maximum of 30 million copper atoms; these could cover only a little more than 1% of its surface. Actually the amount of copper taken up by an erythrocyte must be much less than this, since after exposing a glycerol-copper solution to one lot of cells, which are then quickly removed, its effect on a fresh lot of cells may be only slightly diminished. In 1 such experiment with an initial copper concentration of 6×10^{-7} M it is estimated that each of the first lot of cells could have removed at most 1 million copper atoms which could have covered no more than about $\frac{1}{20000}$ of the total cell surface. Because such a minute fraction of the surface may be involved in a relatively enormous permeability effect, and because this effect is limited to certain kinds of erythrocytes already known to be exceptionally permeable to glycerol, it is tentatively concluded that such cells must possess some special mechanism, of restricted distribution in the cell surface, which in some way facilitates the entrance of glycerol and which is reversibly inhibited by very low concentrations of copper.

The Action Potential of Human Nerve and Muscle, Normally and After Nerve Injury. M. G. LARRABEE, PH.D., and R. HODES, PH.D. (Johnson Foundation, Univ. of Penna.)* *Nerve Action Potentials*. In an attempt to obtain an early prognosis after nerve injury, action potentials were recorded from 31 injured nerves during operative exposure for exploration, neurolysis, or removal of tantalum cuffs.

* Work done under a contract, recommended by the Committee on Medical Research, with the Office of Scientific Research and Development.

For comparison the action potentials were measured in 9 normal nerves, or above the point of injury in regenerating nerves. The normal potentials were all larger than any found in the regenerating portion of a nerve. Technical difficulties, mostly incidental to the necessity of recording from small regenerating fibers in large nerve trunks in continuity, prevented satisfactory observation in about one-third of the injured nerves. In at least 7 other instances no action potential could be detected although the sensations of the patient (under local anesthesia) or the contraction of muscles clearly indicated the presence of functional fibers. It was therefore concluded that technical difficulties plus limitations in sensitivity render the method unsatisfactory for detecting the presence of a small number of functional fibers in a large nerve, and hence of doubtful usefulness for prognosis.

Electromyograms. Muscle action potentials in response to supramaximal percutaneous stimulation of various nerves were recorded in a number of normal individuals and in patients with peripheral nerve injuries. The potentials were recorded through small electrodes on the skin. Suitable electrodes and supports were devised for recording from all the major muscle groups in the hand, forearm, leg, and foot. Control observations were made to determine the limitations of the method, particularly those due to the wide spread of the action potential of each muscle. Decrease in amplitude of the action potential after nerve injury indicates decrease in the number of muscle fibers innervated, while increase in latency of the response indicates slowing of the conduction velocity of the regenerating nerve fibers and therefore a decrease in axonal diameter.

The normal conduction velocities in the median and ulnar nerve fibers supplying the hand muscles and in tibial and peroneal nerve fibers to the foot muscles ranged from 44 to 65 meters per second. After nerve suture and sometimes after spontaneous recovery of nerve function, the velocities were much lower, being

accurately measured at less than 50 % of normal in some cases and estimated to be as low as 5 % to 10 % of normal in others. Velocity appears to increase progressively during the 1st year after suture, but probably never regains more than 60 % of normal. Since velocity is known to be directly proportional to the diameter of an axon, this implies a similar limitation in axonal growth after suture. In contrast, fibers of approximately normal diameter rapidly develop in many cases where regeneration occurs without nerve surgery.

The amplitude of action potential recorded from a given normal muscle is variable (average difference between duplicate determinations = 23 %), and in addition the average amplitude is different for different muscles. In examining muscles whose nerves have been injured, we have routinely expressed the amplitude of the maximal response as a per cent of the maximal action potential of the same muscle in the uninjured extremity of the same individual. After nerve suture muscle action potentials in response to nerve stimulation were first detectable at a time which depended on the distance from lesion to muscle, indicating rates of regeneration in good agreement with the commonly accepted values of 1 to 2 mm. per day. In general, re-innervation could be detected by watching for movement during a voluntary effort of the patient before an action potential could be recognized. For the later stages of recovery, it is convenient to plot the per cent of normal action potential amplitude against the number of months allowed for recovery divided by the distance from the lesion to the muscle. Against this abscissa, recovery was found to occur at more or less comparable rates in various sutured nerves. In comparison those nerves which did not require operation recovered their function at a wide variety of speeds, often much more rapidly than after the most favorable suture. By comparison with data such as this, it should be possible to tell whether recovery

is lagging unduly in any peripheral nerve patient submitted to similar electromyographic examination. It cannot yet be regarded as established, however, that the method adds enough to the usual clinical

examination to justify its extensive adoption, except in cases of hysteria or malin-gering where the normality of the peripheral nerve and muscle can be definitively demonstrated.

BOOK REVIEWS AND NOTICES

RORSCHACH'S TEST. II. A Variety of Personality Pictures. By SAMUEL J. BECK, PH.D., Head of Psychology Laboratory, Department of Neuropsychiatry, Michael Reese Hospital, Chicago; Associate Professor of Psychology, Northwestern University. Foreword by ROY R. DRINKER, LT. COL., M.C. Pp. 402. New York: Grune & Stratton, 1945. Price, \$5.00.

THE purpose of the first volume was to demonstrate the process used in evaluating Rorschach test processes. The present volume is concerned with interpretation: analyses of Rorschach records of certain persons who must remain anonymous. The chapters of Part I are: Concerning Personality, and Psychological Significance of Rorschach Test Factors. Those of Part II are: The Intelligence Curve, The Adolescent Years, Schizophrenic Solutions, Neurotic Struggles, and Before and After: The Tests Repeated in the Same Persons. Beginning with the record and interpretation of an important university president and foremost scientist, the studies include a nurse in training, a mother-son struggle, hebephrenia in an adolescent boy, reaction and recovery in an ex-soldier, a male overt homosexual, together with other important personality pictures.

A principal objection to the Rorschach test has been its tediousness but no satisfactory short-cut has yet been devised. The group method which the writer continues to omit was introduced by Harrower-Erickson in 1941, and has been employed with sufficient promise of success to justify its continuance. In this procedure the blot pictures are projected onto a screen where they are viewed by classes of from 20 to 50 subjects. Certain objections have been raised, some of which are: the responses must be written, each subject receives the same amount of time, handling of the cards is lacking, etc. Subjects who may be unsuited to this method should receive the routine questioning test. Less important workers have sought to improve the originators technique, but not this exponent—he continues to hew

to the line. Through wide experience, a sympathetic and understanding treatment, the writer has given us a book of high merit.
N. Y.

THE PHYSIOLOGY OF THE NEWBORN INFANT. By CLEMENT A. SMITH, M.D., Professor of Pediatrics, Wayne University College of Medicine, Medical Director, The Children's Hospital of Michigan. Pp. 312. Springfield, Ill.: Thomas, 1945. Price, \$5.50.

CONVERSION from intra- to extra-uterine living throws a great strain upon the human infant, at a moment when the organs and their functionings are remote from the stability of adult development. A detailed and scholarly concentrate of what is known concerning the observable facets of this conversion is here presented, filtered and crystallized by the critical mind of an author whose contributions to this field are eminent in their own right.

Successive chapters deal with respiration; circulation; blood; liver function; metabolism and heat regulation; digestion; nutrition; renal excretion; endocrinology; immunology. There are informing summaries of prenatal energy metabolism, intra-uterine respiratory movements, and fetal circulation, and of the adjustments these make to worldly living. Controversial problems receive logical appraisal.

The book is more of a reference than a text. Pediatricians, obstetricians, and other physicians who are discontented with merely conforming to simple rule-of-thumb routines in the care of newborns and prematures will find it an authoritative mine of knowledge and inspiration.
I. W.

MEDICAL CLINICS OF NORTH AMERICA. Boston Number. Specific Methods of Treatment. Pp. 1341. Phila.: Saunders, 1945. Price, \$16.00 a year.

THIS issue is a timely summary of specific methods of treatment. With the recent

advances in specific therapy it becomes increasingly more difficult for the busy practitioner to keep abreast with these developments. This issue gives a concise appraisal of some of these newer advances.

Janeway, Berenberg and Hutchin's Clinic on "Indications and Uses of Blood, Blood Derivatives and Blood Substitutes" is well written, concise, and very informative, as is also the Davies Clinic on "The Treatment of Meningitis." In all this issue is a valuable contribution. J. F.

WHAT THE INFORMED CITIZEN NEEDS TO KNOW. Edited by BRUCE BLIVEN and A. G. MEZERIK. Pp. 377. New York: Duell, Sloan & Pearce, 1945. Price, \$3.00

THE Table of Contents of this timely and wide-embracing book suffices to show why a notice of it is not unsuitable for medical among other citizens.

The United Nations Charter (E. Stettinius, Jr.); America and World Trade (W. Berge); World Industrialization (M. Cooke); Our Relations with Russia (W. Batt); The Inter-American Family (S. Inman); Relief and Rehabilitation (E. Thomas); Jobs for All (H. Wallace); The Threat of Inflation (C. Bowles); Patents and Monopolies (J. O'Mahoney); War Surplus—Tool for Peace (A. Mezerik); *Planning, Liberty, and Security* (A. Hansen); Science and the American Future (B. Bliven); Rivers and Prosperity (L. Hill); Health is Everybody's Business (T. Parran); Good Houses for Everybody (C. Abrams); Tax Policy for a Prosperous America (R. Paul); The Family-Size Farm (J. Patton); Veterans: The Twelve-Million-Man Question (C. Bolte); The Problem of Minorities (C. McWilliams); Which Way Politics? (I. Brant); Labor's New Responsibilities (Philip Murray). E. K.

URANIUM AND ATOMIC POWER. By JACK DE MENT, Research Chemist, The Mineralogist Laboratories, and H. C. DAKE, Editor, The Mineralogist Magazine. With Appendix on the Atomic Bomb. Pp. 335. Brooklyn: Chemical Publishing Co., 1945. Price, \$4.00.

THE release and harnessing of atomic energy has become of such immediate practical importance to everyone—the medical man, scientists in general, and the man on the street—that we are glad to bring this simple presentation to the attention of our

readers. Prepared in 1939, it aimed to present in simple terms the concepts of atomic physics and the available information about uranium. This edition provides in 7 chapters and 8 appendices much of the information on the subject that all but specialists require. The seventh appendix tells in 7 brief pages the events that led to the use of the atomic bomb against Hiroshima—a story that is officially and more fully told in Professor Smyth's report to the War Department (Princeton University Press).

The first 23 pages on the structure of the atom and atomic power possibilities will be found especially useful, also the tabular matter in the first 6 appendices. One learns of the basic work (starting with the stimulus of Einstein's theoretical equation, 1903, and extending over more than a decade) that preceded the first great practical use of atomic power. The internationalism of science is well illustrated by the various rôles played by Rutherford and the British, Hahn and Mietner, Fermi, Urey, Lawrence, Oppenheimer, and others too numerous to mention. The book is timely, and as far as one can judge about matters beyond one's field, appears to be accurate and well put together. There is an adequate bibliography, though one regrets that the index is not more detailed. E. K.

DR. W. C. ROENTGEN. By OTTO GLASSER. Cleveland Clinic Foundation. Pp. 166. Springfield, Ill.: Charles C Thomas, 1945. Price, \$4.50.

THE year 1945 provided the occasion for this double anniversary book, being both the centennial of Roentgen's birth and the semi-centennial of his discovery of the X-ray. It is based largely on the writer's biography, written in 1933, supplemented by a score of subsequent publications, letters and documents. It is a concise, clear, authoritative survey of a life of a great scientist by one who thoroughly knows his subject. *Inter alia* is included the account of Goodspeed's "accidental X-ray photograph" at the University of Pennsylvania in 1890, which however, was never put forward by him as a discovery but merely as "the first picture in the world (taken) by cathodic rays."

A list of Roentgen's 58 scientific papers, a chronology of his life, a Bibliography, and Index add to the usefulness of the book. E. K.

HAHNEMANN. The Adventurous Career of a Medical Rebel. By MARTIN GUMPERT. Pp. 251. New York: L. B. Fischer, 1945. Price, \$3.00.

DURING the author's 10 years in this country, he has combined the work of a busy practice with the successful completion of several entertaining books about medicine. This book, also, will be found entertaining and interesting, not only because of a lively, humorous and challenging style but also because it deals with a remarkable person. However, the author's attitude toward homeopathy, especially as expressed in the 4 pages of the "Prologue" indicates, to the Reviewer at least, that he misinterprets the rôle that homeopathy plays and has played or else that entertainment comes first in his desiderata. The Reviewer realizes that he has thus exposed himself to the same sort of criticism that is so vividly and sharply expressed in the Prologue, though he too would criticize the attitude of "the celebrated professor of internal medicine" therein portrayed. Also, the Reviewer recognizes, as he has expressed elsewhere, that homeopathy was helpful earlier in correcting therapeutic abuses and that some current practices have a superficial similarity to *similia similibus*. Nevertheless, he is far from agreeing that "a number of the most important, and newly discovered, methods of treatment . . . had been anticipated in the works of Hahnemann," he knows of no homeopathic universities in North America, and even the homeopathic medical schools have been so forced by circumstances to change their curriculum and practices that their differences from regular schools now are negligible and soon will be non-existent. In this country at least, there is no danger that in this field strife will "forever overwhelm friend and foe," because homeopathy, having made its contribution to the great stream of medical progress, is on its way out as a separate discipline. This, however, need not spoil for the reader a good story well told.

E. K.

MICROBES OF MERIT. By OTTO RAHN, Professor of Bacteriology, Cornell University. Pp. 277. Lancaster: Jacques Cattell, 1945. Price, \$4.00.

In his foreword, the author states that an enthusiastic picture of bacteria other than pathogens is needed, especially for the lay-

man, who generally thinks all bacteria are harmful. He goes about this by giving a brief but interesting historical account of bacteriology. The main part of the book is devoted to a discussion of what microbes are and how valuable they are to man. He presents a wealth of information in an interesting manner, including the useful rôle of microbes in the production of sauerkraut, vinegar, beer and wine, alcohol, buttermilk, cottage cheese, and antibiotics such as penicillin and streptothricin. The illustrations include several humorous but purposeful cartoons. The last chapter is an epilogue in which the author suggests that a world without microbes would not be very pleasant. The book is divided into 22 chapters as follows: 1. The Smallest Beings on Earth. 2. The Discovery of Bacteria. 3. Amazing Appetites. 4. The Relatives of Bacteria. 5. Bacteria Divide When They Multiply. 6. Bacteria Can Be Tough. 7. Contamination. 8. Bacteria Among Themselves. 9. From Dust to Dust. 10. Bacteria Help the City People. 11. Bacteria Help the Farmer. 12. The 1941 Census of Bacteria. 13. Domesticated Yeasts. 14. When Bacteria Blunder. 15. Microbes and Our Daily Bread. 16. Compromise Between Man and Microbe. 17. Microbes the Food of the Future. 18. Man a Parasite of Bacteria. 19. Industry Harnesses Bacteria. 20. Inheritance Among the Sexless. 21. Bacteria Replace Guinea Pigs. 22. The World Without Microbes. E. L.

PEDIATRIC X-RAY DIAGNOSIS. A Textbook for Students and Practitioners of Pediatrics, Surgery and Radiology. By JOHN CAFFEY, A.B., M.D., Associate Professor of Pediatrics, College of Physicians and Surgeons, Associate Pediatrician and Roentgenologist, Babies Hospital and Vanderbilt Clinic, New York City; etc. Pp. 838. Chicago: The Year Book Publishers, 1945. Price, \$12.50.

ANY one who has had occasion to look for authoritative guidance on some puzzling or questionably abnormal feature of a child's roentgenogram knows that (if he has been genuinely in earnest) the search for references begins with a patient survey of the *Index Medicus*, and ends with a resigned acceptance of the fact that the articles on the particular subject are scattered through a diversity of unrelated periodicals, of which

only a minority of those desired are to be found in any one hospital library. It is 35 years since publication of the last book in English on pediatric roentgen diagnosis.

For this reason, and also because of its excellence and completeness, this new text book by Caffey is to be greeted warmly and enthusiastically. Here, unified under one cover, is a great body of essential information, representing the experience, studies and interpretive analysis of one of the world's experts in this expansive field. The book is simply written, remarkably well-organized, and liberally illustrated with half-tone reproductions, linear tracings, and schematic teaching diagrams. A small list of amplifying references closes each discussion. The descriptions of growth phenomena are especially fine. Every pediatrician, radiologist, surgeon and practitioner who has to cope with diagnostic problems related to childhood should have this book for handy reference.

I. W.

WHAT PEOPLE ARE. A Study of Normal Young Men. By CLARK W. HEATH. Pp. 141. Cambridge: Harvard University Press, 1945. Price, \$2.00.

THE reader who takes this title at face value will be disappointed. If he is wise enough to read the excellent preface by Arlie Bock, he will realize that the aim is not to tell us what people are, but to outline a program of study of this complex matter in order to indicate the approach that is being made to questions of great practical importance to which the answers must await the maturity of the boys who are studied. Present conclusions are necessarily tentative. The work is based upon the correlation of diverse techniques to achieve a comprehensive survey of each individual. These include a social study of family background, psychologic, psychiatric, physiologic, and anthropologic analyses. We await the sequel with interest.

G. McC.

MEDICAL CLINICS OF NORTH AMERICA. Philadelphia Number. Symposium on Gynecology and Obstetrics. Phila: W. B. Saunders, 1945. Price, \$16.00 a year.

THIS volume is a symposium on recent advances in gynecology and obstetrics, prepared principally by the staffs of the Philadelphia Lying-in Hospital and Medical Col-

lege Hospital. It contains 20 reports upon a wide variety of topics. It includes among its topics of current interest: (1) some recent laboratory procedures of current interest; (2) the management of the syphilitic pregnant woman with special reference to the use of penicillin; (3) a discussion of single dose and continuing spinal anesthesia for labor and vaginal delivery; (4) the timing of ovulation by basal temperature graphs. This volume would seem to have special value for the physician just returning from the armed forces and for anyone in general practice.

D. M.

THE BACTERIAL CELL IN ITS RELATION TO PROBLEMS OF VIRULENCE, IMMUNITY, AND CHEMOTHERAPY. By RENE J. DUBOS, George Fabyan Professor of Comparative Pathology and Professor of Tropical Medicine and Public Health, Harvard University, and member of the Rockefeller Institute. With an Addendum by C. F. ROBINOW, Strangeways Laboratory, Cambridge, Eng. Pp. 460; 33 ill. Cambridge, Mass.: Harvard University Press, 1945. Price, \$6.00.

By reviewing much of the recent literature on bacterial anatomy and physiology, the author presents a correlation, as far as existing data permit, of ideas and facts concerning bacterial make-up and function. Knowledge about bacterial structure is gained directly from study of stained preparations, dark-field microcinematography, and electron microscopy. Chemical and serologic studies have yielded information concerning cellular components. In some instances such procedures indicate actual morphologic positions of these products such as capsular antigens or somatic surface antigens. A study of bacterial enzyme systems leads to knowledge of microbial function. The known relationships between bacterial variability and enzyme activity variation are considered. The author minutely discusses the use of the term, "virulence," in relation to pathogenic bacteria and their hosts. The problem of bacterial dissociation applied to immunization procedures, or the use of isolated bacterial antigens for the same purpose in man and animals, entails not only a discussion of the development of type specific immunity but also a consideration of the relatively little studied group specific or broadly specific

immunity. The probable mechanisms of action of bacteriostatic agents, particularly the sulfonamides, are developed here in moderate detail. Such discussions of the chemotherapeutic agents fit into the theme of the book through their ability to inhibit bacterial function and enzymes, or to cause dissociation. In attempting to correlate the observations of many investigators on bacterial structure and properties the author incorporates the opinions of those whose work he cites as well as his own. The Addendum by C. F. Robinow presents detailed considerations of bacterial structures of somewhat controversial nature, such as the problem of the bacterial nucleus. Throughout the book, evidence from the literature in support of statements is presented in the form of numerous charts, figures, and photographs. The bibliography is extensive and broad in scope. This book can be recommended particularly for those persons working in the fields of bacteriology or investigative preventive medicine as well as for students entering the fields. J. F.

TEXTBOOK OF MEDICINE. Edited by J. J. CONYBEARE, M.C., D.M., Oxon., F.R.C.P., Physician of Guy's Hospital, London. Seventh Ed. Pp. 1164. Baltimore: Williams & Wilkins, 1945. Price, \$8.00.

THE 1945 edition of Conybeare's Textbook of Medicine compares unfavorably with the available textbooks of medicine by American authors. The first item contributing toward this unfavorable impression was the absence of 4 pages from the Table of Contents of the reviewer's copy. A more important defect was a failure of the contributors to include recent medical advances in their discussion. In the field of chemotherapy the sulfonamides did not receive the attention they deserved; it is amazing to realize that sulfadiazine is little known in Britain and not readily available. Sulfamerazine is unmentioned and readers are referred to the literature for information on penicillin.

Many other sections were notably deficient. The diseases of the thyroid gland and liver were not brought up to date. In the cardiologic section it was surprising to find the value of precordial electrocardiography questioned, and the drug, aminophyllin, apparently unknown and unused.

One amusing item, for American readers at least, was the use of the 14 pound archaic

"stone" as a unit of weight in the discussion of diabetes.

In no part of the book is the reader furnished with references for the material presented and he is left with the feeling that most of the statements are based on clinical impression rather than on controlled observations by the authors or others. In all of the presentations, there is very little correlation between pathologic and physiologic changes.

R. M.

THE CARE OF THE NEUROSURGICAL PATIENT—Before, During and After Operation. By ERNEST SACHS, A.B., M.D., Professor of Clinical Neurological Surgery, Washington University School of Medicine, St. Louis. Pp. 268; 177 ills., including 2 in color. St. Louis: C. V. Mosby Co., 1945. Price, \$6.00.

THE vast experience of the dean of American neurologic surgeons has been utilized in the preparation of this monograph. The career of Dr. Sachs, extending through the entire period of modern neurosurgery, is reflected in this book; it is of great value to younger men to be informed of the various stages of growth through which neurosurgical technique has passed.

The precise details of examination, of preoperative care, of the various operative procedures, and of the postoperative problems are presented. The discussion of such points as the proper position for the patient, the diet, the care of the bowels, use of medications, dressing of wounds, etc., will be welcomed by the new resident in neurologic surgery. Features in the care of the unconscious or uncoöperative patient, seldom presented in other texts, receive adequate consideration here. A more detailed discussion of cerebral edema and measures to combat this principal postoperative difficulty, such as by ventricular puncture, should perhaps have also been included.

The more experienced neurosurgeon will appreciate the description given of Dr. Sachs' operating clinic and technique, from which many points gained through years of trial and elimination are made available for the reader's consideration. The chapter on anesthesia is not as complete as one might wish, and no longer do all neurosurgeons or anesthesiologists share the enthusiasm for avertin expressed in this book.

This well written and well illustrated con-

cise monograph can be heartily recommended to all interested in this subject. It will, of course, be of principal value to those just embarking on their careers in neuro-surgery.

F. G.

FUNDAMENTAL PRINCIPLES OF PHYSICAL CHEMISTRY. By CARL F. PRUTTON, PH.D., Professor of Chemistry and Chemical Engineering, and SAMUEL H. MARON, PH.D., Associate Professor of Physical Chemistry, Case School of Applied Science, Cleveland, Ohio. Pp. 780. New York: Macmillan, 1944.

THIS new book is primarily intended as a textbook for a full year course in physical chemistry for chemistry and chemical engineering students. As such it of course covers completely all aspects of the subject. Much, but not all, of the material would be applicable to a shorter course such as is often given to students in the various branches of the biological sciences. As the authors suggest, it can be adapted for such a course by judicious selection of subjects. They do not however suggest any program but leave details to the instructor.

The authors have made no radical innovations in presenting their material. Major topics covered are gases, liquids, solids, solutions, colloids, thermochemistry, electrolytic phenomena, ionic equilibrium, kinetic reactions, atomic and molecular structure and the correlation of such structure with physical and chemical properties. The text is well organized and well written. At the end of each chapter is a short useful bibliography. The printing and binding are good, indeed better than most wartime offerings. Certainly this book can be well recommended as a text for students of chemistry and allied sciences.

W. S.

WHAT TO DO ABOUT VITAMINS. By ROGER J. WILLIAMS. Pp. 56. Norman: University of Oklahoma Press, 1945. Price, \$1.00.

THE discoverer of Pantothenic Acid has written a very interesting and informative book about what he has called "food lubricants," i. e., the vitamins and minerals, in contrast to the "food fuels."

The volume adds to the sources available for intelligent readers who want to know more about diet and health. Aids to teaching the subjects are numerous and original.

E. W.

HEMATOLOGY FOR STUDENTS AND PRACTITIONERS. By WILLIS M. FOWLER, A.B., M.D., Professor of Internal Medicine, University of Iowa, Iowa City. With a chapter by ELMER L. DEGOWIN, A.B., M.D., Assistant Research Professor of Medicine, University of Iowa, Iowa City. Pp. 499; 8 plates, 110 figs. New York: Hoeber, 1945. Price, \$8.00.

THIS is a good, practical text for students and practitioners, written by a careful, conscientious, able teacher. The essentials of clinical hematology are well presented. The color plates are excellent and most of the photomicrographs and other figures are complementary and illuminating. The chapter by Dr. Degowin on transfusion is especially up-to-date and authoritative. A few minor errors of omission and commission might be mentioned, and a "watch-dog" type of critic might raise the question of the over-all need for this latest hematologic text book. This reviewer, however, likes this book and recommends it to sophomore and senior medical students and to returning veteran medical officers and other practitioners who want a sound review of the old and an introduction to the new in clinical hematology.

T. F.-H.

CLASSIC DESCRIPTIONS OF DISEASE. With Biographical Sketches of the Authors. By RALPH H. MAJOR, M.D., Professor of Medicine, University of Kansas School of Medicine. Pp. 679. Springfield: Charles C Thomas, 1945. Price, \$6.50.

As our previously expressed praise (AM. J. MED. SCI., June, 1933 and April, 1939) of this valuable book remains unchanged, we content ourselves with noting the following major (no pun intended!) additions: Hodges, N., *Loimologia*; Nott, J., *Yellow Fever Contrasted With Bilious Fever*; Home, F., *An Enquiry Into the Nature, Cause and Cure of the Angina Suffocativa*, etc.; Cober, T., *The Hungarian Disease*; Louis, Pierre, *The Disease Known Under the Names of Gastro-enteritis, Putrid, Adynamic, Ataxic, Typhoid Fever*, etc.; Vieusseux, G., *Cerebral Malignant Non-contagious Fever*; North, E., *Malignant Epidemic Commonly Called Spotted Fever*; Hippocrates, *Mumps*; DaCosta, J., *On Irritable Heart*; Riverius, L., *Caruncles Resembling a Cluster of Hazelnuts*; Battista, G., *Excrescences on the Valves*; Bouillaud, J.,

Confluent Vegetations on the Valves; Virchow, R., *Concerning Acute Inflammation of the Arteries*; Kirkes, W., *Detachment of Fibrinous Deposits From the Interior of the Heart*; Winge, E., *Mycosis endocardii*; Vitry, J., *A Certain Pestilence*; Sire de Joinville, J., *The Army Sickness*; Aretaeus, *On the Coeliac Affection*; Heberden, W., *Of the Nyctalopia or Night-Blindness*; Graves, R., *Fugitive Inflammation*.

There is a welcome addition of an 11-page bibliography which gives from 1 to 13 references each, on 179 celebrities. The thinner paper used—perhaps unavoidably—gives a smaller, lighter volume, to be sure, but also a sheet that is less easily read and more prone to wrinkle. E. K.

NEW BOOKS

Manual of Diagnosis and Management of Peripheral Nerve Injuries. By ROBERT A. GROFF, M.D., LT. COL., M.C., A. U. S., formerly Assistant Professor of Surgery, Jefferson Medical College, and Assistant Professor of Neurosurgery, Graduate School of Medicine, University of Pennsylvania, and SARA JANE HOUTZ, B.S., 1ST LIEUT. (P.T.) A. U. S. With an Introduction by I. S. RAVDIN, M.D., BRIG. GENERAL, M.C., A. U. S., John Rhea Barton Professor of Surgery, University of Pennsylvania. Pp. 188; 111 ills. Phila.: Lippincott, 1945. Price, \$8.00.

An Introduction to Physical Anthropology. By M. F. ASHLEY MONTAGU, Associate Professor of Anatomy, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania, Visiting Lecturer, Department of Sociology, Harvard University. Pp. 325. Springfield, Ill.: Thomas, 1945. Price, \$4.00.

A Future for Preventive Medicine. By EDWARD J. STIEGLITZ, M.S., M.D., F.A.C.P. Pp. 73. New York: The Commonwealth Fund, 1945. Price, \$1.00.

The Psychoanalytic Theory of Neurosis. By OTTO FENICHEL, M.D. Pp. 703. New York: W. W. Norton & Company, Inc., 1945. Price, \$7.50.

War Neuroses. By ROY R. GRINKER, LT. COL., M.C., and JOHN P. SPIEGEL, MAJOR, M.C., Army Air Forces. Pp. 145. Phila.: The Blakiston Co., 1945. Price, \$2.75.

Everybody's Way to Health and Fitness. By T. R. TOGNA. The Influence of Exercises in the Bath on the Circulatory and Respiratory Systems. With Introductions by SIR LEONARD HILL, M.B., F.R.S., LL.D., formerly Director, Department of Allied Physiology and Hygiene, National Institute of Medical Research, London, and DR. JENNER HOSKIN, M.D., F.R.C.P. London: The Caxton Press, Ltd., 1945. Price, 5s.

Sir Leonard Hill says in his Introduction, "The attention of physio-therapeutists might well be directed to Mr. Togna's work. . . . He has proved the great value of such exercises, and were they widely practised a great deal of rheumatic pain and disability together with cardio-vascular disease in old age might be prevented."

Advances in Protein Chemistry. Volume II. Edited by M. L. ANSON, Continental Foods, Hoboken, and JOHN T. EDSALL, Harvard Medical School, Boston. Pp. 443. New York: Academic Press, 1945. Price, \$6.50.

Pathology in Surgery. By N. CHANDLER FOOT, M.D., Professor of Surgical Pathology, Cornell University Medical College, Surgical Pathologist, New York Hospital. Pp. 511; 368 ills. Phila.: Lippincott, 1945. Price, \$10.00.

Advances in Carbohydrate Chemistry. Volume I. Edited by W. W. PIGMAN, Corn Products Refining Co., Argo, Ill., and M. L. WOLFROM, The Ohio State University, Columbus, Ohio. Pp. 374. New York: Academic Press, 1945. Price, \$6.00.

Men Without Guns. Text by DEWITT MACKENZIE, War Analyst of The Associated Press. Descriptive Captions by MAJOR CLARENCE WORDEN, Medical Department of the United States Army. Foreword by MAJOR GENERAL NORMAN T. KIRK, Surgeon General of the United States Army. Pp. 152; 137 ill. Phila.: Blakiston, 1945. Price, \$5.00.

Clinical Roentgenology of the Heart. (Annals of Roentgenology) Volume XVIII. By JOHN B. SCHWEDEL, M.D., Asso. Attending Physician, Medical Division, Adjunct Attending Physician, Dept. of Roentgenology, Montefiore Hospital, New York, etc. Pp. 380; 749 ills. New York: Paul B. Hoeber, 1945. Price, \$12.00.

NEW EDITIONS

American Red Cross First Aid Textbook.

Prepared by the American Red Cross for the Instruction of First Aid Classes. Revised with 264 ills. Pp. 254. Phila.: Blakiston, 1945.

This edition of the well-known textbook for "first-aiders" has had the advantage of the

close coöperation and supervision of experts of the Division of Medical Sciences of the National Research Council and of profiting by the experiences—military and civilian—of World War II. The results appear in many of the pages and illustrations. It is a much more practical as well as up-to-date book than the 1937 edition ever was.

E. K.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in *THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES*, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in *THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES* exclusively, except in the case of subsequent publication in Society proceedings.

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WITH this volume *THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES* changes its size for the first time in its existence of 125 years. The reasons for this are twofold. Of chief concern to the reader is that the greater width of the printed page permits the use of double columns, which expert investigations have shown to be easier than a single column on the eye and attention of the reader. Secondly, a number of medical advertisers have agreed among themselves to furnish cuts in 3 sizes only, so that our longer, wider page will conform to their medium size cut. We regret the passing of the journal's distinctive size, but hope that its equally distinctive yellow cover will long be maintained. It may be of interest to note here that when the supply of yellow cover papers was recently exhausted and could not be renewed, it was found desirable to preserve the familiar "Yellow Journal" by printing white paper in yellow, though this required two passages through the press.

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The American Journal of the Medical Sciences

Due to the increased costs of material and labor, we find it necessary to increase the subscription price of *THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES* to \$7.00 per annum. This is the first increase in price since 1920, when it cost \$5.00 a year, the price that was established at its origin in 1820.

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We regret the necessity of making this change in price and we shall thank you for your continued patronage.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MARCH, 1946

ORIGINAL ARTICLES

THE INVASIVE CHARACTER OF CANCER GROWTH*

BY DALE REX COMAN, M.D.

PHILADELPHIA, PENNSYLVANIA

(From the Department of Pathology, University of Pennsylvania Medical School)

As my subject deals with the invasive character of cancer growth, it is well first to consider precisely what is meant by the term invasiveness.

Let me begin by reminding you that all tumors consist of cells derived from the body tissues. A tumor might be defined for our purposes as an excessive and limitless local multiplication of cells. This local multiplication leads to the formation of a lump, a swelling, a tumor.

Tumors may be divided into two main groups, benign and malignant. Benign tumors remain strictly localized; they are circumscribed and sharply demarcated from the surrounding normal tissues. Frequently a capsule forms around them, serving as a sort of mantle that separates the tumor cells within from the normal cells outside. As the cells of the benign tumor multiply the tumor grows larger, but its growth is expansive, like a balloon being inflated with air. Thus the benign tumor merely compresses and pushes aside the surrounding normal tissues.

Malignant tumors, however, do not remain strictly localized. The cells of the malignant tumor infiltrate and permeate into the surrounding parts. There is no capsule, or only an incomplete one. As the cells multiply the tumor increases in size, but not like a balloon expanding; rather,

like the roots of a plant penetrating the soil. The cells of the malignant tumor disrupt the surrounding tissue, dislocating the normal cells and often destroying them. The cancer cells may even gain entrance to a blood vessel or a lymphatic vessel in this way and so be swept into the general circulation and then be deposited in some distant part of the body. Becoming established there by their continued multiplication they produce a secondary tumor, or metastasis.

It is this invasive type of growth which concerns us now. Upon what does this invasiveness depend? Why do benign tumor cells remain localized? What is it that enables malignant cells to penetrate the surrounding parts?

First, it is not the presence of a capsule that makes the benign tumor remain localized. Sometimes a benign tumor becomes malignant. When it does, it expresses its malignancy by invading through the capsule. The capsule, then, is no barrier to the invading cancer cells.

It was suggested long ago that malignant tumor cells might secrete some substance that would destroy the adjacent normal tissues, without injuring the tumor cells. Such heterolytic ferments were, indeed, reported by several investigators.^{1,8,13,14} Further work,^{10,12} however, did

* An address before the Philadelphia Chapter of the Sigma Xi, November 28, 1945.

not substantiate these reports and today this hypothesis is no longer seriously considered by most investigators.

A third attempt to explain invasive growth suggested that the tumor cells were forced into the surrounding tissues because of the pressure built up within the tumor by the proliferating mass of cells.⁶ The tumor thus supposedly broke through its bonds and penetrated neighboring parts. The cells, once free, might further invade by their own ameboid movement. But this mechanism does not explain why benign tumors do not invade. Benign tumors may grow as large as malignant ones, and frequently become even larger because they do not invade and kill the host. Where one incises a benign tumor, often it bulges outward, indicating that the cells within the tumor were under considerable pressure, yet they were not forced out into the neighboring tissues.

This attempt at explanation, then, does not fit the facts. It remains true, however, that *mechanical stresses and tensions do explain the mechanism of displacement of cells, once they are free to be displaced*. Benign tumor cells are evidently bound in some way so that they are incapable of displacement, in contrast to malignant cells which are free. Because it is free, the malignant cell can be displaced mechanically or wander off by ameboid movement.

I shall mention a fourth explanation only because it has been frequently repeated. The statement is made that "Malignant cells invade because they have escaped from the formative influences of the neighboring tissues." This is obviously no explanation at all, because the term "formative influences" lacks definite meaning. It would obstruct further investigation if we folded our hands in acceptance of such a statement.

It has been suggested that the malignant tumor is invasive because its growth is peripheral;^{7,9} that is, the cells of the tumor which multiply are at the edges of the tumor instead of at the center as in benign tumor. But mitotic activity occurs throughout both benign and malignant

tumors. It becomes less conspicuous in the central part of any tumor, benign or malignant, in which part the blood supply is reduced by the increasing size of the tumor. This suggestion, then, is not a satisfactory explanation of invasive growth.

To summarize at this point:

The benign tumor does not remain localized because of the presence of a capsule.

The suggestion that malignant cells secrete destructive ferments has not been supported by evidence.

The explanation that malignant cells are forced into the neighboring tissues by pressure within the tumor, due to cell multiplication, leaves unanswered the question, why then do benign tumors not invade?

The explanation that malignant cells have escaped "local formative influences" is no explanation at all.

Last to be mentioned, the suggestion that invasiveness depends upon peripheral cell multiplication in malignant tumors, whereas proliferation in benign tumors is central, fails because multiplication occurs in both types throughout.

What other possibilities are there?

A year or so ago the following observation was made.⁴ An attached pair of fresh living cancer cells from a man's lip were examined with a micromanipulator. One micro needle was inserted into one of the cancer cells, the other into the other cell. The needles were then moved gradually apart. It was noted that the cancer cells separated, one from the other, very easily. But when a pair of normal cells from the lip were treated in the same way, they clung to each other tenaciously.

This observation suggested a possible solution of our problem. If it were found that malignant cells were indeed easily separable one from the other, it would offer a physical basis for invasive growth. Such easily detached cells would then be free for mechanical displacement into the surrounding tissues, or free to wander off by their own locomotion.

Therefore, a large number of cells was

examined with the micromanipulator. Cells were obtained from cancers of the lip, from normal lips, from cancers of the cervix, from normal cervixes and from papillomas of the skin (benign tumors). The technique was refined so that the force required to pull apart a pair of cells could be measured. This was accomplished by measuring the bend produced in a microneedle as it pulled a pair of cells apart. One stiff unbending needle held one of an attached pair of cells. The tip of the other needle was inserted into the other cell. This latter needle was flexible and had been calibrated previously with micro-weights, so that it was known that a given force would produce a certain amount of bending. By measuring the amount of bend in the needle, the force necessary to pull a pair of cells apart was obtained. The results of this investigation are shown in Table 1. Malignant cells, whether from the lip or cervix consistently showed low values of cohesiveness as compared with normal and benign tumor cells.

TABLE 1.—FORCES REQUIRED TO SEPARATE PAIRS OF CELLS BY MICROMANIPULATION

Derivation of cells	Mean and its standard error, mg.	
Normal lip	1.42	± 0.041
Carcinoma, lip	0.47	± 0.051
Papilloma, skin	1.25	± 0.032
Normal cervix	1.11	± 0.039
Carcinoma, cervix	0.18	± 0.022

Each figure is based upon 50 pairs of cells and represents the mean (with its standard error) of the force in mg. required to separate the cells by micromanipulation. It is seen that the values for carcinomatous cells are much lower than those for normal cells and for cells from papillomas.

Thus it would seem from these observations that cancer cells are indeed less firmly attached to one another than are normal or benign tumor cells, and as mentioned before, this offers a physical basis for invasive growth.

But, we must go further. Upon what does this cohesiveness of cells depend? It seems most likely that it must in some way depend upon the state of the cement substance that is known to exist between cells and which serves to bind them together. Can we find any differences between be-

nign and malignant tumor cells in regard to this cement substance?

Two possible explanations will be presented. The first of these we shall call the calcium deficiency hypothesis.

Biologists have known for a long time that calcium plays a part in maintaining the cohesiveness of cells. Cells which normally stick tightly together will separate readily if calcium is withdrawn from the medium in which the cells are immersed. The stability of the intercellular cement substance is thus dependent upon the presence of calcium.¹⁵

Supposing then that it could be shown that cancers were deficient in calcium, this might lessen the cohesiveness of the cells and lead to invasive growth as suggested above.

Carruthers and Suntzeff³ applied a carcinogenic chemical to the skin of mice. They then measured the calcium content of the normal skin of mice and compared it to the calcium content of the skin after treatment with the chemical carcinogen. They found that soon after the application of the carcinogen, the calcium content dropped. Another large drop in calcium occurred when the skin cells became truly cancerous and invasive. Furthermore a group of human cancers was analyzed by Scott¹⁶ who found that they were deficient in calcium. This calcium deficiency in cancer bearing patients is a local deficiency, confined to the tumor; the blood level of calcium in cancer patients is not disturbed.

The calcium deficiency hypothesis, then, finds support in the chemical analysis of cancer tissue. It may be the answer to our question, though it leaves for the future the next question, why do cancer cells contain less calcium?

The second possible explanation of the decreased cohesiveness of cancer cells we shall call the increased spreading factor hypothesis.

It is a property of some substances⁵ to enhance the spread or diffusion of small particles or solutions through living tissues. Such substances are called spreading

factors. A very potent spreading factor is an enzyme called hyaluronidase, which can be extracted from testicular tissue. If a solution of hyaluronidase is mixed with India ink and then injected into the skin of a rabbit it causes the ink particles to spread widely through the skin. The action of hyaluronidase is to hydrolyze hyaluronic acid,¹¹ one of the chief constituents of the intercellular cement substance, thereby separating the cells and allowing the ink particles to pass between them.

Is it possible that some such mechanism as this plays a part in causing the decreased cohesiveness of cancer cells? If so, cancers should have a high content of spreading factor.

Boyland and McClean² determined the spreading factor content of a large group of animal tumors. These tumors ranged from benign, non-invasive tumors to malignant, invasive cancers. They reported that the spreading factor content paralleled the malignancy of these tumors; the more malignant the tumor the more spreading factor it contained.

This result would certainly seem to lend support to the hypothesis that the decreased cohesiveness of cancer cells depends upon an excessive amount of spread-

ing factor. Furthermore, if this substance were released by the cancer cells it might act upon the cement substance of the adjacent normal tissues, thus facilitating the invasion of the normal tissues by the cancer cells. The work of Boyland and McClean has not as yet been confirmed elsewhere. A similar analysis of human tumors is under way in our laboratory at the present time, but has not progressed sufficiently far to allow conclusions to be drawn.

This discussion began with a single question, upon what does the invasive growth of cancer depend? Instead of a single answer, I must close with several questions.

Does the decreased cohesiveness of cancer cells depend upon the local calcium deficiency that is known to exist in cancer tissue? Or, does it depend upon a local increase in spreading factor? May it not in some way depend in part upon each of these factors? Perhaps the actions of calcium, hyaluronic acid, and hyaluronidase are in some way connected in regulating the consistency of the cement substance. And finally, are there any other ways in which the invasive growth of cancer cells can be explained?

REFERENCES

1. BLUMENTHAL, WOLFF: *Ergebn. d. Exp. Path. u. Ther.*, **1**, 65, 1907.
2. BOYLAND, E., and MCCLEAN, D.: *J. Path. and Bact.*, **41**, 553, 1935.
3. CARRUTHERS, C., and SUNTZEFF, V.: *Science*, **99**, 245, 1944.
4. COMAN, D.: *Cancer Res.*, **4**, 625, 1944.
5. DURAN-REYNALS, F.: *Bact. Rev.*, **6**, 197, 1942.
6. EWING, J.: *Neoplastic Diseases*, 3d ed., Philadelphia, Saunders, p. 506, 1934.
7. EWING, J.: *Neoplastic Diseases*, 3d ed., Philadelphia, Saunders, p. 31, 1934.
8. JACOBY: *Hoffmeister's Beitr.*, **3**, 446, 1903.
9. KARSNER, H.: *Human Pathology*, 6th ed., Philadelphia, Lippincott, p. 273, 1942.
10. KEPINOW: *Ztschr. f. Krebsforsch.*, **7**, 517, 1909.
11. MEYER, K., CHAFFEE, E., HOBBY, G. L., and DAWSON, M. H.: *J. Exp. Med.*, **73**, 309, 1941.
12. MILLER, ED.: *Deutsch. Arch. f. klin. Med.*, **92**, 199, 1908.
13. NEUBERG: *Berl. klin. Wchnschr.*, **41**, 1080, 1904.
14. NEUBERG: *Ztschr. f. Krebsforsch.*, **2**, 171, 1904.
15. ROBERTSON, J. D.: *Biol. Rev.*, **16**, 106, 1941.
16. SCOTT, G. H.: *Biol. Symp.*, **10**, 277, 1943.

MULTIPLE PULMONARY HEMANGIOMATA

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WITHIN recent years, the attention of medical men has been increasingly directed to diseases of the chest by the advent of successful thoracic surgery. Because of the increasing interest in the accurate diagnosis of intrathoracic lesions, we are reporting, in this paper, a new case of pulmonary hemangioma. The previously reported cases of this condition, 7 in number,^{2-4,6-9} will be briefly reviewed in order to call attention to the fact that pulmonary hemangioma produces so characteristic a syndrome that it may be strongly suspected from clinical evidence alone.

In 1938, Rodes reported the first case of pulmonary hemangioma with polycythemia and other evidences of chronic anoxemia.⁸ The patient had died of massive hemorrhage apparently spontaneous in nature, and the lesion was demonstrated postmortem. The fact that this condition is truly rare, and that the paucity of reports is not merely the result of faulty diagnosis, is indicated by the fact that large series of routine autopsies throughout the world make no mention of this condition.

A pulmonary hemangioma (also called pulmonary arteriovenous fistula) is a knot of blood vessels connected by feeder vessels with both the pulmonary arterial and venous circulations. Thus it acts as a shunt whereby blood can pass from the arterial to the venous circulations of the pulmonary circuit without passing through the lungs and being oxygenated. The physiologic effect of this is to produce a low oxygen saturation of the arterial blood supply; all other changes are secondary to this anoxemia. The tumors themselves are cavernous hemangiomata, benign in nature.

Case Report. In November of 1944, the descriptions of pulmonary hemangiomata that had appeared in the literature since 1938^{3,4,6,7,8,9} called to mind a patient seen in 1941. This young man was asked to present himself for further examination. He is native born of Italian descent, who was a patient of Dr. Jacob Makler in 1941. At that time he was 17 years old. His complaints of 3 years duration, were marked cyanosis and mild dyspnea on exertion. His family history was negative. He was not a "blue baby" at birth. There had been no severe pulmonary disease in infancy and there had never been a history of rheumatic fever. He had never lived at high altitudes. There had never been known exposures to silver salts, arsenic, aniline, manganese, or coal tar derivatives. His growth and development had been normal. Physical examination revealed an asthenic but normally built man. He had marked cyanosis. The fingers were markedly clubbed. The lungs and heart were completely normal to examination. Neither the liver nor the spleen were palpable. Temperature, pulse and respiration were normal and the blood pressure was within normal limits. The laboratory studies and special examinations done at this time are presented in Table 1. There was slight polycythemia. The white count, venous pressure, circulation times and electrocardiogram were all normal. A Roentgen ray of the chest was interpreted as showing increased vascular shadows probably due to the polycythemia. Otherwise the film was normal. The patient was discharged with the diagnosis of congenital heart disease, probably intra-auricular septal defect; but, it was understood at the time, the diagnosis was not satisfactory because a right to left shunt sufficient to cause marked cyanosis should cause murmurs, evidence of right ventricular enlargement or other signs of cardiac disease.

In 1941 a Roentgen ray of the chest was taken as a follow-up procedure. The film

was reported by Dr. Arthur Finklestein as showing increased hilar markings probably due to the polycythemia. A note was made to the effect that the shadows might be caused by the presence of abnormal blood vessels, but no further attention was paid to this possibility.

When the patient returned to us in November 1944, he reported that he had had no new symptoms since his previous admission with the exception of occasional nosebleeds and headaches. The cyanosis, clubbing and dyspnea were very prominent but he did not think that they were becoming worse. He was leading a normal life and was attending college at the time. The physical examination was very much the same as on the first admission with two exceptions. A small telangiectasis was present behind the right ear and a systolic murmur was heard in the left fourth interspace, 5 cm. to the left to the mid-sternal line. The great possibility is that the telangiectasis was missed on his first physical examination, but we have no way of telling whether or not the murmur is a recent development.

Roentgen Findings. In our original examination in 1941, a fairly discrete opacity measuring approximately 2 cm. in diameter was noted in the mid-portion of the right lung field at the level of the eighth rib posteriorly. A second poorly defined, irregular opacity measuring 3 cm. in diameter was noted in the seventh posterior interspace in the mid-portion of the left lung. From each of these opacities, a broad linear shadow was seen extending towards the hilum. The roentgen interpretation, at this time, was that the changes noted were due to thrombotic vessels secondary to the polycythemia. We were not satisfied with this interpretation and reexamination at a future date was suggested for comparison.

Eight months following the original study, the patient returned and was re-rayed. There was no significant change in the previously described lesions. The heart was again of normal size and configuration. At this time possibility of angioma was suggested although the original diagnosis was not changed.

The present studies, done in November 1944, showed two additional masses similar to those previously described. They lay in the right lung and one was well down into the shadow of the diaphragm. The heart

was still normal in size and configuration. The originally described opacities were again seen. The linear shadows extending to the hilum were interpreted as feeder vessels to the angiomatous masses. During the chamber analysis, under fluoroscopic observation, the intrathoracic pressure was altered by asking the patient to try to expire with the mouth closed and the nostrils occluded (Valsalva experiment), and then to try to inspire under the same conditions. These efforts resulted in a marked decrease and then increase in the size of the masses and feeder vessels, as the negative pressure was made lower and then increased. Repeated attempts at long exposure films were not successful in demonstrating pulsation of the masses. Laminographic studies were then done to clearly delineate the areas involved. The shadows extending from the hilar region were seen to be dilated pulmonary vessels. The lung field masses presented an irregular worm-like configuration that was continuous with the feeder vessels (see illustration). These findings confirmed the previous impression of multiple pulmonary hemangiomata.

It will be seen (Table 1) that there had been progression of the abnormal findings present on the first admission. The red count and hemoglobin were higher. The circulation times were slower, as would be expected in view of the increased red cell count. The sternal marrow aspiration showed a slight tendency to overactivity of erythropoiesis. The ratio of red cells to white cells was about 1:1, and this is the upper limit of normal for the red series. The marrow, in general, was normally cellular.

In summary, then, we had a young man in good health except for polycythemia and the signs and symptoms referable to it. These were cyanosis, clubbing of fingers, headache, easy fatigue, nosebleed, and slight dyspnea on exertion.

In addition, he had a peculiar murmur in the fourth interspace 5 cm. to the left of the mid-line, and had a small telangiectasis behind one ear.

At the time of this writing, November 1945, the patient has remained clinically unchanged since his last hospital admission a year ago.

Differential Diagnosis. The causes of polycythemia may be given as:

1. Polycythemia vera
2. Secondary polycythemia
 - a. High altitude
 - b. Poisoning by heavy metals or aniline dyes
 - c. Pulmonary disease preventing adequate oxygenation
 - Ayerza's disease
 - Emphysema
 - d. Cardiac anomalies with a right to left shunt
 - Tetralogy of Fallot
 - Complex of Eisenmenger
 - Pulmonary artery stenosis with septal defect
 - e. Pulmonary hemangioma

all indicate that the polycythemia is secondary rather than primary.

Considering the list of causes of secondary polycythemia, we were able to eliminate several items by history alone. The patient had never dwelt at high altitudes; and, in any case, it has been demonstrated⁵ that the polycythemia caused by this practice persists for only a short time after the subject has returned to sea level. Poisoning by heavy metals or aniline dyes was very unlikely since the patient was aware of no prolonged exposure to these substances. The prolonged course of illness is also against such poisoning being causative. The possibility of the

TABLE 1.—LABORATORY STUDIES

	September 11, 1941	November 18, 1944
Red cell count	6,200,000	7,700,000
Hemoglobin	17 gm.	19.5 gm.
White blood count	7900	6500
Polymorphonuclears	67%	69%
Eosinophils	1%	0%
Basophils	0%	0%
Lymphocytes	28%	28%
Monocytes	4%	3%
Hematocrit	Not done	55
Platelet	Not done	175,000 (normal for this lab.)
MCV	71 μ
MCH	27 γ	25 γ
MCHC	35%
Venous pressure	125 mm.	125 mm.
Calcium time	14 sec.	20 sec.
Ether time	9 sec.	14 sec.
Sternal marrow	Not done	
Erythrogonos		2
Normoblasts A		5
Normoblasts B		11
Normoblasts C		26
		— Total R.B.C. 44
Blasts		1
Promyelocytes		1
Myelocytes		7
Metamyelocytes		17
Mature polymorphonuclears		19
Eosinophils		3
Monocytes		2
Megakaryocytes		0
Lymphocytes		6
		Granulocytes 50
		Lymphocytes 6
		100

In the case of our patient, there was almost nothing to suggest a diagnosis of polycythemia vera. His youth, the lack of splenomegaly, the normal range of the white cell and platelet counts, and the lack of hyperplasia of the white cell progenitors and megakaryocytes in the bone marrow

existence of chronic pulmonary disease was next to be considered. Such disease might well account for the anoxemia that stimulates the marrow to produce abnormally large numbers of red cells. Our patient had a normally shaped thorax with ample and symmetrical expansion during

inspiration. The diaphragm appeared on physical examination to descend amply. The breath sounds were normal throughout the chest and there was no alteration of the percussion note. Roentgen examination, including fluoroscopy confirmed these findings. Furthermore, the absence of right ventricular enlargement on physical examination, on electrocardiographic examination and on Roentgen ray study was strongly against any great amount of emphysema or Ayerza's disease.

that cause anoxemia, cyanosis, clubbing and polycythemia are those associated with a very large shunt of blood from the right side of the heart or great vessels to the left side without the blood passing through the lungs. It has been estimated¹⁰ that 30% of the blood must pass through such a shunt in order for cyanosis to occur. Conditions that might cause such a deviation in the normal blood flow are absence of the interventricular septum, gross septal defects with pulmonary sten-

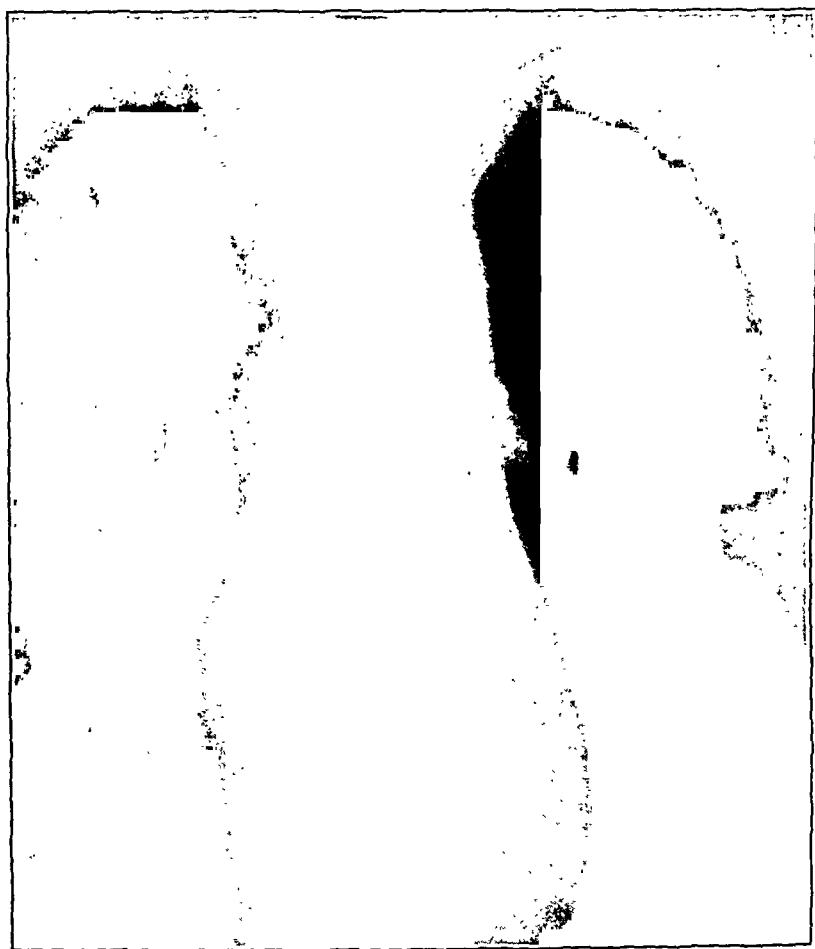


FIG. 1.—Laminographic Roentgen ray: a pulmonary hemangioma is seen in the left lung field with its feeder vessel going to the hilum. A descending feeder vessel is poorly seen in the right lung field, paralleling the mediastinal shadow.

Perhaps the most difficult and important cause of polycythemia to rule out was congenital heart disease. Here again we were forced to utilize negative findings for the most part. The congenital heart lesions

osis, and transposition of the great vessels. In all these conditions, one obtains a history of cyanosis from birth, the patient's growth and development are often seriously impaired, and cardiac enlarge-

ment with preponderance of the right ventricle is demonstrated by physical examination, Roentgen ray of the chest and right axis deviation on the electrocardiogram. Furthermore characteristic murmurs can usually be demonstrated. The absence of the above named factors made it seem very unlikely that congenital heart disease was the cause of our patient's secondary polycythemia.

The elimination of the usual causes for polycythemia left us with strong suspicion that pulmonary hemangioma was the correct diagnosis. Accordingly, Roentgen ray confirmation was sought by means of fluoroscopy and laminography as well as the customary technique for chest films. The complete report appears in the case report.

mention the red count. None of the 7 cases have had demonstrable heart or lung disease. Three of the 7 cases had multiple pulmonary hemangiomata, our case having the largest number. Four of the 7 cases had demonstrable hemangiomata elsewhere. Hemorrhage occurred in 2 of the cases and has also been reported as the cause of death in an infant who had a pulmonary hemangioma and died at such an early age that the picture of the chronic condition could not occur.²

Discussion. In view of the results in the other cases of this disease, the prognosis must be accepted as grave, with the danger of massive hemorrhage always present. Even if this does not occur, polycythemia is a condition that is associated with serious complications. Exhaustion of the

TABLE 2.—ANALYSIS OF 7 REPORTED CASES

Cases reported	(1)	(2)	(3)	(4)	(5)	(6)	Present case
Age	25	40	23	22	30	24	20
Dyspnea	+	+	+	+	+	+	+
Clubbing	+	+	+	+	+	+	+
Cyanosis	+	+	+	+	+	+	+
Hemangiomata elsewhere	+	0	0	+	+	0	+
Cardiac disease	0	0	0	0	0	0	0
Lung disease	0	0	0	0	0	0	0
R.B.C. in millions	7.5	6.5	9.5	11.5	..	7.5	7.7
Number of lung hemangiomata	3	1	1	1	3	1	4
Hemorrhage	+	0	0	0	+	0	0
Course	Death from hemorrhage	Well	Pneumectomy, well	Well	Multiple excision after hemorrhage, well	Pneumectomy, well	Well

Review of Previously Reported Cases. So few cases of this nature have been reported that this summary can draw no sweeping conclusions. A reference to Table 2 will show that the cases have been remarkably similar. We believe that this similarity is so striking that a definite clinical picture may be said to exist. In view of the far greater frequency of congenital cardiac lesions as a cause for polycythemia and cyanosis in the young, pulmonary hemangioma can only be kept in mind until the heart has been ruled out as the source of trouble. All the cases reported have been young adults. Dyspnea, clubbing, cyanosis and polycythemia have been common to all, although the case of Janes⁶ does not

marrow with anemia, granulocytopenia, thrombocytopenia or any combination of these conditions may occur. It has been stated that leukemia or erythroleukemia is a complication of polycythemia, but this is not generally accepted. A peripheral blood picture resembling chronic myelogenous leukemia can occur when the marrow becomes exhausted and myeloid metaplasia of the spleen occurs. Under such circumstances, nucleated red cells, and immature white cells, including myelocytes, may appear in the blood. These factors, plus the anemia and thrombocytopenia and the enlarged spleen, cause a superficial resemblance to chronic myelogenous leukemia. However, the marrow

shows exhaustion and aplasia instead of the hyperplastic state seen in leukemia.

In any polycythemic patient, thrombosis is a great danger and may even cause death. The increased viscosity of the blood, which results from increase in the red cell mass without adequate concomitant increase in the plasma,⁵ results in slowing of the circulation and an increased tendency to clot.

It must also be considered that the increased viscosity of the blood causes an abnormal burden to be placed upon the heart.

Lastly, duodenal ulcer is found commonly in patients together with polycythemia,¹ and the latter may possibly predispose a patient to the former by producing vascular changes and plugging of small vessels in the intestinal wall.

In view of all these factors, it is probable that surgery is the best method of handling cases of this disease. The extent and type of the surgery naturally depend upon the particular case. Local excision, lobectomy and pneumonectomy are all possible. In the patient with whom we are now concerned, the multiplicity of the lesions, and their bilateral distribution, make operation hazardous. The patient has been informed of the situation and does not wish surgery at this time. The possibility of operation is still being considered for some

future time. No attempts to depress the formation of red cells by Roentgen ray, radioactive phosphorus or other methods are contemplated, since their efficacy is questioned and their risk is not. Phlebotomy for the relief of symptoms will be undertaken if there continues to be progression of the polycythemia, headache, and so forth.

Summary. A case of pulmonary hemangioma is presented with a clinical picture sufficiently typical for a clinical diagnosis to be made. An examination of the sternal marrow, and a fluoroscopic study of the pulmonary lesions are reported. We believe this to be the first time these procedures have been done in a case of this nature. The changes in the lesions during a Valsalva experiment are of particular interest, being reported for the first time.

The literature on this subject is briefly summarized. The importance of thorough Roentgen ray study in assessing the nature and extent of the lesion is emphasized. It is stressed that this lesion should be carefully sought for in obscure cases of polycythemia, cyanosis, hemoptysis, murmurs, or abnormal shadows on Roentgen ray, since surgical cure can be effected in a fair number of instances. A brief discussion of the differential diagnosis and complications of polycythemia is included.

REFERENCES

1. BOCKUS: *Gastroenterology*, vol. 1, p. 575, Philadelphia, Saunders, 1944.
2. BOWERS: *Nebraska Med. J.*, 21, 55, 1936.
3. GOLDMAN, A.: *Dis. of Chest*, 9, 479, 1943.
4. HEPBURN, J., and DAUPHINEE, J. A.: *AM. J. MED. SCI.*, 204, 681, 1942.
5. HURTADO, MERINO, DELGADO: *Arch. Int. Med.*, 75, 284, 1945.
6. JAMES, R.: *Brit. J. Surg.*, 31, 270, 1944.
7. JONES, J. C., and THOMPSON, W. P.: *J. Thorac. Surg.*, 13, 357, 1944.
8. RODES, C. B.: *J. Am. Med. Assn.*, 110, 1914, 1938.
9. SMITH, H. L., and HORTON, B. T.: *Am. Heart J.*, 18, 589, 1939.
10. WHITE, P. D.: *Heart Disease*, New York, Macmillan, 1944.

EFFECT OF STREPTOMYCIN ON EXPERIMENTAL BRUCELLOSIS
IN GUINEA PIGS*

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THERE is no known effective treatment of brucellosis. In discussing the use of sulfonamides in veterinary practice, Stableforth⁷ states that they have not been found of value in the treatment of *Brucella abortus* infections, and according to our own experience, the administration of sulfapyridine⁴ and sulfathiazole⁵ to cows suffering with brucellosis was ineffective. Keefer³ in reviewing recently the status of penicillin in the treatment of infections, lists *Brucella* among the microorganisms which are not susceptible to the action of this antibiotic substance. On the other hand, streptomycin,⁶ a substance isolated from *Actinomycetes griseus*, has been found by Jones, Metzger, Schatz and Waksman² to protect chick embryos against infection with *B. abortus*. On the basis of these findings it was decided to investigate the effect of streptomycin on experimental infection of guinea pigs with *B. abortus*.

EXPERIMENT 1. Eighty guinea pigs were infected with *B. abortus*; 40 were then treated with streptomycin, and the others served as controls. Each of the guinea pigs was injected subcutaneously with 20,000 *B. abortus* as determined by plate counts which represented at least 1000 infective doses because 2 guinea pigs injected at the same time with a 1000-fold dilution of this concentration, *i. e.*, 20 *Brucella* cells, were positive on cultures when autopsied 4 weeks later. The culture used was an anaerobic strain of *B. abortus* which was originally

isolated from the milk of a naturally infected cow, and was subsequently passed through guinea pigs four times, thus enhancing its virulence. Finally, the culture was lyophilized to preserve its virulence, and was subcultured 48 hours prior to infection of the animals. The weights of the guinea pigs before infection ranged between 350 and 500 gm., and they were weighed weekly following infection.

Dosage. In treating tuberculosis in guinea pigs, Feldman and Hinshaw¹ found that the more purified the streptomycin the better it was tolerated by the animals, and they used daily doses ranging from 1750 to 6000 units.† Throughout this experiment the treated guinea pigs received 5000 units daily divided into 5 equal doses. Each dose of the material was dissolved in 1 ml. of sterile distilled water, and the injections were made subcutaneously at 3-hour intervals beginning at 9 A.M. and ending at 9 P.M. each day. Administration of streptomycin to 20 guinea pigs was begun 3 hours after infection, and to 20 other guinea pigs 1 week after infection.

Studies in Vitro. By keeping the number of *B. abortus* organisms constant (approx. 10 million) and varying the concentration of streptomycin, it was found that 1.2 units were required per ml. of tryptose agar or tryptose broth to inhibit completely the growth of the organisms. In addition, this concentration of streptomycin in tryptose broth proved definitely

* These studies were supported by funds from the Pennsylvania Department of Agriculture and the Bureau of Animal Industry, United States Department of Agriculture. The streptomycin was provided through the courtesy of Merck & Co.

† A unit of streptomycin is that quantity of the antibiotic agent which inhibits the growth of a given strain of *Escherichia coli* in 1 ml. of nutrient broth or agar.

bactericidal because no growth was obtained when 0.5 ml. quantities of the broth-streptomycin-*Brucella* mixture were subcultured on pour plates after 18 hours incubation, while subcultures of the controls yielded an abundance of growth. Similar results were obtained with the use of a 100-fold dilution of the organisms (approx. 100,000), which would indicate that when a sufficient quantity of streptomycin was present in the culture medium, it killed a high as well as a low concentration of *Brucella* organisms. Five strains of *B. abortus*, 3 aerobic and 2 anaerobic ones, were thus tested, and no appreciable difference was noticed in the mode of streptomycin action upon them.

Toxicity. The animals tolerated the streptomycin well, and no general or local toxic effects were noticed in connection with the administration of the material. There were some slight differences in the weight increase of the animals in the various groups at the end of 4 weeks; *i. e.*, the average gain in weight per guinea pig in the group treated for 27 days was 89.5 gm.; in the group treated for 20 days, 108.6 gm.; and in the non-treated infected group, 85.9 gm. Hemoglobin determinations on the blood prior to autopsy of the animals showed an average of 13.5 gm. of hemoglobin per 100 ml. of blood in the treated groups, and 13.6 gm. per 100 ml. of blood in the untreated infected controls.

Results of Therapy. The administration of streptomycin was discontinued 27 days after infection. Thus, one group of 19 guinea pigs (one animal died of intercurrent disease), had been treated for 27 days and another group of 20 guinea pigs for 20 days. Blood was obtained for agglutinative tests and hemoglobin determinations 24 hours after cessation of treatment from 9 guinea pigs which had been treated for 27 days, from 10 guinea pigs which had been treated for 20 days and from 19 controls, and then these animals were killed and their tissues cultured. Eight days after therapy was discontinued, blood was obtained from the remaining animals, and then they were killed and their tissues cul-

tured. In each instance one of the inguinal lymph glands and pieces of liver and spleen were cultured by rubbing the cut surface of each tissue over a separate tryptose agar plate, and the plates were incubated under 10 per cent CO₂ tension for 5 days. One treated guinea pig and 3 controls died of intercurrent disease during the early part of the experiment, and are, therefore, not included in the discussion. Table 1 contains the results of the agglutinative tests and the culture findings of the animals killed 1 day after discontinuation of treatment. While the agglutinative titers of the controls ranged from 1:100 to 1:400, the sera of 12 of the treated animals were negative in a 1:25 dilution. Furthermore, the control guinea pigs yielded *Brucella* on cultures in each instance, whereas 4 of the animals treated from the day of infection, and 4 in which treatment was begun one week after infection were negative on cultures. Six of the remaining treated guinea pigs yielded *Brucella* from 1 or 2 tissues only, and in 5 animals *Brucella* was isolated from all 3 tissues. However, the *Brucella* colonies isolated on culture plates from the treated animals were much fewer in number than in the case of the untreated controls. In Table 2, are presented the data on the animals killed 8 days after cessation of treatment. The blood sera of six of the guinea pigs treated from the day of infection were negative in a 1:25 dilution when tested against *Brucella* antigen. The tissues of 3 of these were negative on cultures, and 2 additional animals yielded only 1 and 2 *Brucella* colonies, respectively. All the guinea pigs in which treatment was begun 1 week after infection, and all the controls were positive to the agglutinative test and on cultures.

EXPERIMENT 2. Since the quantities of streptomycin used in the first experiment, namely, 5000 units daily, did not produce visible toxic effects, another group of animals was subjected to treatment with larger doses of this antibiotic substance.

Ninety-three guinea pigs were each injected subcutaneously with 2840 *B. abortus* of the same anaerobic strain as was used

in the first experiment. One week after infection treatment was begun on 40 guinea pigs, and the other 53 animals were left as controls. Throughout this experiment the treated guinea pigs received 20,000 units of streptomycin daily divided into 6 equal doses, and the injections were made subcutaneously at 3-hour intervals beginning at 9 A.M. and ending at 12 midnight each day.

Toxicity. No general toxic effects were noticed as a result of the injections of streptomycin. Toward the latter part of the experiment, however, thickening of the skin and subcutaneous tissue was observed in 6 animals in the region in which most of the injections were made, namely, the ventral side of the thorax and abdomen, and at autopsy these animals showed adhesions between the cutis and subcutis.

TABLE 1.—RESULTS OF AGGLUTININATIVE TESTS AND CULTURE FINDINGS ON GUINEA PIGS AUTOPSIED ONE DAY AFTER DISCONTINUATION OF TREATMENT

Treated animals*						Controls					
Guinea pig No.	Treatment begun	Length of treatment	Agglutinative titer at time of autopsy	Culture findings			Guinea pig No.	Agglutinative titer at time of autopsy	Culture findings		
				I.L.G.	L.	S.			I.L.G.	L.	S.
1	On day of infection	27 days	P 1:25	—	—	+	40	P 1:100	+	+	—
2			Neg.	+	—	+	41	P 1:200	+	+	+
3			Neg.	—	—	—	42	P 1:100	+	+	+
4			Neg.	—	—	—	43	P 1:200	+	+	+
5			Neg.	—	—	—	44	P 1:100	+	+	+
6			P 1:50	+	+	—	45	P 1:200	+	+	+
7			Neg.	—	—	—	46	P 1:200	+	+	+
8			Neg.	—	—	+	47	P 1:400	+	+	+
9			P 1:50	+	+	+	48	P 1:200	+	+	+
10			Neg.	—	—	—	49	+ 1:200	+	+	+
11	1 wk. after infection	20 days	Neg.	—	—	+	50	P 1:200	+	+	+
12			Neg.	+	—	+	51	P 1:200	+	+	+
13			P 1:50	+	+	+	52	P 1:400	+	+	+
14			Neg.	—	—	—	53	+ 1:200	+	+	+
15			P 1:50	+	+	+	54	P 1:400	+	+	+
16			Neg.	—	—	—	55	P 1:200	+	+	+
17			P 1:200	+	+	+	56	P 1:400	+	+	+
18			P 1:100	+	+	+	58	P 1:400	+	+	+
19			Neg.	—	—	—	59	+ 1:200	+	+	+

* Each animal received 5000 units streptomycin daily divided into 5 equal doses which were injected subcutaneously at 3 hour intervals between 9 A.M. and 9 P.M.

Agglutinative tests: Neg. = negative in 1:25 dilution; P = incomplete agglutination; + = complete agglutination.

Culture findings: I.L.G. = inguinal lymph gland; L = liver; S = spleen; + = positive; — = negative.

TABLE 2.—RESULTS OF AGGLUTININATIVE TESTS AND CULTURE FINDINGS ON GUINEA PIGS AUTOPSIED 8 DAYS AFTER DISCONTINUATION OF TREATMENT

Treated animals*						Controls					
Guinea pig No.	Treatment begun	Length of treatment	Agglutinative titer at time of autopsy	Culture findings			Guinea pig No.	Agglutinative titer at time of autopsy	Culture findings		
				I.L.G.	L.	S.			I.L.G.	L.	S.
20	On day of infection	27 days	Neg.	—	—	+	60	P 1:100	+	+	+
21			P 1:25	+	+	+	61	P 1:800	+	+	+
22			P 1:50	+	+	+	62	P 1:200	+	+	+
23			Neg.	—	—	+	63	P 1:200	+	+	+
24			P 1:25	+	+	+	64	P 1:100	+	+	+
25			P 1:25	+	+	+	65	P 1:400	+	+	+
26			Neg.	+	+	+	67	P 1:200	+	+	+
27			Neg.	—	—	—	68	P 1:200	+	+	+
28			Neg.	—	—	—	69	P 1:50	+	+	+
29			Neg.	—	—	—	70	P 1:400	+	+	+
30	1 wk. after infection	20 days	P 1:400	+	+	+	71	P 1:200	+	+	+
31			P 1:50	+	+	+	73	P 1:200	+	+	+
32			P 1:100	+	+	+	74	P 1:400	+	+	+
33			P 1:100	+	+	+	75	+ 1:200	+	+	+
34			P 1:100	+	+	+	76	P 1:400	+	+	+
35			P 1:100	+	+	+	77	P 1:200	+	+	+
36			+ 1:800	+	+	+	78	P 1:100	+	+	+
37			P 1:100	+	+	+	79	P 1:400	+	+	+
38			P 1:50	+	+	+					
39			P 1:100	+	+	+					

* Each animal received 5000 units streptomycin daily divided into 5 equal doses which were injected subcutaneously at 3 hour intervals between 9 A.M. and 9 P.M.

† Only 1 colony present.

‡ Only 2 colonies present.

Agglutinative tests: Neg. = negative in 1:25 dilution; P = incomplete agglutination; + = complete agglutination.

Culture findings: I.L.G. = inguinal lymph glands; L = liver; S = spleen; + = positive; — = negative.

Hemoglobin determinations on the blood prior to autopsy of the animals showed an average of 12.71 gm. of hemoglobin per 100 ml. of blood in the treated groups, and 13.27 gm. per 100 ml. of blood in the controls.

continued, at which time 35 treated guinea pigs and 29 controls were still alive. Twenty-four hours after cessation of treatment blood was obtained for agglutinative tests and hemoglobin determinations from 17 treated animals and 11 controls, and

TABLE 3.—RESULTS OF AGGLUTININATIVE TESTS AND CULTURE FINDINGS ON GUINEA PIGS USED IN EXPERIMENT 2

Treated animals*						Controls		
Guinea pig No.	Treatment begun	Length of treatment	Autopsied after cessation of treatment	Agglutinative titer at time of autopsy	Culture findings	Guinea pig No.	Agglutinative titer at time of autopsy	Culture findings
81	1 wk. after infection	24 days	1 day	Neg.	—	121	P 1:50	+
82				Neg.	—	122	P 1:50	+
83				Neg.	+	124	Neg.	+
84				Neg.	++	127	P 1:100	+
85				Neg.	—	128	P 1:100	+
86				Neg.	—	129	P 1:200	+
87				Neg.	—	131	P 1:50	+
88				Neg.	—	134	P 1:100	+
89				P 1:25	+	138	P 1:25	+
90				Neg.	+	139	P 1:50	+
92				Neg.	—	141	+ 1:50	+
93				Neg.	—			
95				Neg.	—			
96				Neg.	—			
97				Neg.	—			
98				Neg.	—			
99				Neg.	—			
100				Neg.	—	143	P 1:400	+
101				Neg.	—	146	P 1:400	+
102				P 1:50	+	147	P 1:200	+
104			8 days	Neg.	—	148	P 1:400	+
105				Neg.	—	149	P 1:100	+
106				P 1:50	+	151	P 1:400	+
107				Neg.	—	153	P 1:400	+
109				Neg.	—	154	P 1:400	+
110				Neg.	—	156	P 1:100	+
111				Neg.	—	159	P 1:400	+
112				Neg.	—	160	P 1:400	+
113				Neg.	—	161	P 1:400	+
114				Neg.	—	165	P 1:200	+
115			15 days	Neg.	—	166	P 1:100	+
117				Neg.	—	168	P 1:100	+
118				Neg.	—	169	P 1:200	+
119				Neg.	—	172	P 1:200	+
120				P 1:50	+	174	P 1:400	+

* Each animal received 20,000 units streptomycin daily divided into 6 equal doses which were injected subcutaneously at 3 hour intervals between 9 A.M. and 12 midnight.

† Only 1 colony isolated from all 3 tissues.

Agglutinative tests: Neg. = negative in 1:10 dilution; P = incomplete agglutination; + = complete agglutination.

Culture findings: — = negative; + = positive.

Results of Therapy. A protracted cold spell during the early part of the experiment favored a respiratory disorder in most of the guinea pigs, which resulted in the death of 5 treated guinea pigs and 25 controls. The fact that a much smaller percentage of treated guinea pigs succumbed would lead one to suspect that the streptomycin might have helped to keep respiratory infections down in this group of animals.

At the end of 24 days of treatment, which was 31 days after infection, the administration of streptomycin was dis-

then they were killed and their tissues cultured. Eight days after discontinuation of therapy 10 more treated and 10 control guinea pigs were bled and their tissues cultured, and finally 15 days after cessation of treatment the remaining 8 treated animals and 8 controls were bled and their tissues cultured. The technique for culturing the tissues at autopsy was the same as in Experiment 1.

The results of this experiment are presented in Table 3. Of the 17 treated guinea pigs sacrificed 1 day after cessation of treatment, 4 animals yielded *B. abortus* on

cultures, and only 1 of these had detectable agglutinins in a 1:25 dilution of the blood serum. In the group of 10 treated guinea pigs autopsied 8 days after discontinuation of therapy 2 animals were positive on cultures, and had slight agglutinative titers; in the group of 8 treated guinea pigs autopsied 15 days after treatment was discontinued only 1 animal had a slight agglutinative titer and yielded *B. abortus* on cultures. On the other hand, all the controls were positive and *B. abortus* was

continued. These findings assume additional significance in view of the fact that the treatment was not begun until 1 week after infection, by which time the organisms had ample time to multiply and disseminate throughout the body. The 2840 *Brucella* cells injected into each animal represented at least 200 minimal infective doses because a guinea pig injected at the same time with 14 organisms, according to plate counts, was positive on cultures when autopsied 4 weeks after infection.

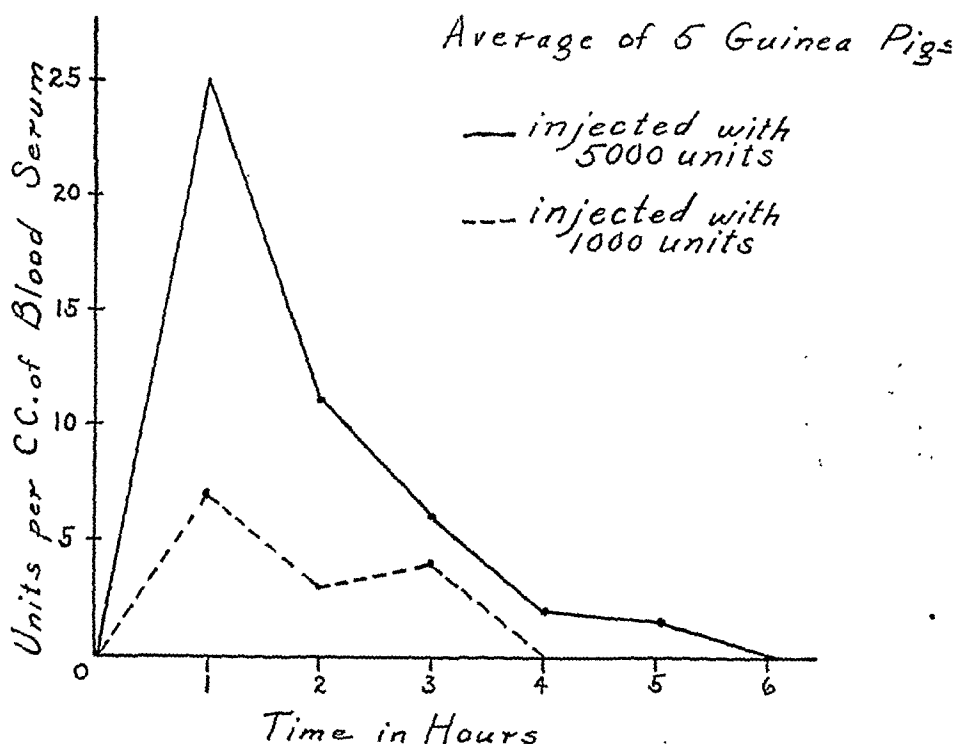


FIG. 1.—Concentration of streptomycin in blood serum of guinea pigs after a single subcutaneous injection.

isolated from all 3 tissues cultured. These results would indicate that contrary to the findings in the first experiment the percentage of treated animals which was positive to the agglutinative test and on cultures was not augmented with an increase in the interval after the time of cessation of treatment. Thus it would appear that the larger doses of streptomycin used in this experiment destroyed the *Brucella* organisms in most of the animals, and their tissues remained sterile when cultured 15 days after therapy was discon-

Concentration of Streptomycin in the Blood Serum Following a Single Subcutaneous Dose. Two groups of 5 guinea pigs each were used to determine the concentration of streptomycin in the blood serum following a single subcutaneous injection of the drug. In one group, each animal received 5000 units of streptomycin while in the other each animal was injected with 1000 units of streptomycin. The animals were bled by cardiac puncture at hourly intervals for 6 hours, and the concentration of streptomycin in the blood sera was de-

terminated by the plate cup method described by Stebbins and Robinson.⁸ As indicated in Figure 1 the average concentration of streptomycin in the blood sera of each group reached its peak after 1 hour, being 25 units per cc. of blood serum in the group injected with 5000 units, and 7 units per cc. of blood serum in the group injected with 1000 units. Then the drug concentration decreased, and no streptomycin could be detected after 4 hours in the blood sera of the animals injected with 1000 units, and none could be detected after 6 hours in the blood sera of the animals injected with 5000 units.

Summary. Treatment of guinea pigs with 5000 units of streptomycin daily, divided into 5 doses, had a definite bacteriostatic effect upon *B. abortus*.

Four of 9 animals in which treatment was begun on the day of infection and continued for 27 days, and 4 of 10 animals in which treatment was begun 1 week after infection and continued for 20 days, were negative on cultures when autopsied 1 day after cessation of treatment. Of the guinea pigs which were cultured 8 days after discontinuation of therapy, 3 animals from the group of 10

in which treatment was begun on the day of infection were still negative while all the guinea pigs in which treatment was begun 1 week after infection yielded *B. abortus*.

Treatment of guinea pigs with 20,000 units of streptomycin daily, divided into 6 doses, seemed to eliminate the infection from most of the animals. The treatment was begun 1 week after infection, and was continued for 24 days. Of 17 animals autopsied 1 day after cessation of therapy, 4 were positive on cultures; of 10 animals autopsied 8 days after cessation of treatment, 2 were positive on cultures, and of 8 guinea pigs autopsied 15 days after discontinuation of therapy only 1 animal yielded *Brucella* on cultures.

Following a single subcutaneous injection of streptomycin, the blood serum levels are highest soon after injection of the drug. In guinea pigs injected with 1000 units no detectable concentration of streptomycin was found in the blood serum after 4 hours, and in those injected with 5000 units no detectable concentration of streptomycin was found in the blood serum after 6 hours.

REFERENCES

1. FELDMAN, W. H., and HINSHAW, H. C.: Proc. Staff. Meet. Mayo Clinic, 19, 593, 1944.
2. JONES, I., METZGER, H. J., SCHATZ, A., and WAKSMAN, S. A.: Science, 100, 103, 1944.
3. KEEFER, C. S.: AM. J. MED. SCI., 210, 147, 1945.
4. LIVE, I., STUBBS, E. L., and GARDINER, M. R.: Am. J. Vet. Res., 4, 276, 1943.
5. LIVE, I., STUBBS, E. L., and GARDINER, M. R.: North Am. Vet., 24, 661, 1943.
6. SCHATZ, A., BUGIE, E., and WAKSMAN, S. A.: Proc. Soc. Exp. Biol. and Med., 55, 66, 1944.
7. STABLEFORTH, A. W.: Vet. Record, 57, 3, 1945.
8. STEBBINS, R. B., and ROBINSON, H. J.: Proc. Soc. Exp. Biol. and Med., 59, 255, 1945.

THE TREATMENT OF ACUTE RHEUMATIC FEVER WITH LARGE DOSES OF SODIUM SALICYLATE

WITH SPECIAL REFERENCE TO DOSE MANAGEMENT AND TOXIC MANIFESTATIONS*

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THE use of large doses of sodium salicylate in treating acute rheumatic fever has received new impetus since the report of Coburn⁴ of the favorable results observed with this form of therapy. Coburn has postulated that with sufficiently high plasma salicylate levels, the sterile rheumatic inflammatory process can be suppressed and subsequent permanent valvular heart damage can be prevented.

We have attempted to evaluate our results with this method of treatment in 18 adults and 8 children with acute rheumatic fever. A variety of interesting metabolic and toxic reactions attributable to salicylate medication, were observed in our patients. Seven persons with diseases other than acute rheumatic fever were given large doses of salicylates for many weeks to examine further the effects of this drug.

Coburn stated that for effective therapy in rheumatic fever, the plasma salicylate level must be maintained above 350 μg . per cc. He has recommended 10 gm. of sodium salicylate and 6 gm. of sodium bicarbonate daily in divided doses for oral medication. During the first 2 weeks of treatment, he preferred to use intravenous medication in the form on a single daily infusion of 10 gm. of the drug or rarely 20 gm. in two separate infusions. The drug was then administered orally. In his group of patients receiving intravenous and subsequently oral medication as well as in the group receiving only oral salicy-

lates, the observed clinical results were excellent.

Material and Results. ADULT GROUP. Our adult group consisted of 10 males and 8 females whose ages ranged from 16 to 46 years. Six were experiencing their first attack of rheumatic fever, 3 others, their second attack and the remaining 9 had had at least 3 episodes prior to the present one. In 11 of the 18 patients, there was a history of an upper respiratory infection preceding the present illness. Thirteen patients had swollen tender joints while 4 others had arthralgia. Fever at the time of admission, was present in 16 cases. In only 5 patients was there a family history of rheumatic fever.

In 5 of the 6 cases with presumably initial attacks of rheumatic fever, there was evidence of cardiac involvement as indicated by apical systolic murmurs in 3 cases, pericardial friction rubs in 2 cases, and abnormal electrocardiographic findings in 5 instances. All 12 patients with recurrent rheumatic attacks, had evidence of structural injury to the mitral valve or to both aortic and mitral valves. Other manifestations of cardiac injury in the 12 patients included cardiac enlargement (8 cases), signs of mild cardiac failure (6 cases), pericardial friction rubs (3 cases) and abnormal electrocardiographic findings (9 cases).

Examination of the blood at the time of entry disclosed significant anemia (volume of packed red cells 30 to 38 cc. %)

* Aided in part by grants from the Physicians' Research Fund of the University of Utah School of Medicine and the Fluid Research Fund of the Rockefeller Foundation.

in 11 of the 18 cases. Leukocytosis was present in 16 patients. The corrected sedimentation rate (Wintrobe method) was greatly elevated in all but one patient in whom it was normal. In this case, however, the leukocyte count was 16,000 per cmm.

In 11 patients, therapy with large doses of salicylates was initiated within 1 to 14 days after the onset of arthritis. In the other 7 patients, medication was not begun until 3 to 14 weeks after the onset of symptoms. In 12 patients, an intravenous infusion of 10 gm. of sodium salicylate was employed on the 1st day of therapy. In 5 patients, this was continued for 3 to 14 days and then oral medication was begun. In the other instances, the oral route was maintained throughout. In 17 patients, salicylate therapy was continued for 4 to 14 weeks while in 1 patient, death occurred from heart failure on the 8th day of medication.

During salicylate administration, clinical and laboratory evidences of rheumatic activity appeared to vanish in the 6 patients with initial attacks and in 5 of the 12 adults with recurrent episodes. In other patients there was usually some improvement but certain findings indicated that active infection persisted.

In every one of the 18 patients, rapid symptomatic improvement occurred within a few days after therapy was begun. In no case was there fever after the end of the 2d week. The pulse rate where it was elevated at the time of admission, usually returned to a normal range by the end of 2 weeks. Joint symptoms subsided within 3 to 6 days and in no case did they recur during therapy. In 8 patients, there was a marked improvement in nutritional status during the period of hospitalization as evidenced by a gain in weight ranging from 8 to 20 pounds (3.6 to 9.1 kg.). Two patients developed beta-hemolytic streptococcal pharyngitis during treatment; nevertheless there was no apparent activation of the rheumatic process.

Pericardial friction rubs which were audible in 5 of the cases at the time of admis-

sion, disappeared in 4 cases within 4 days and in 1 case, only after 2 weeks of medication. A decrease in intensity of cardiac murmurs was noted in the 3 patients with initial attacks in whom murmurs were present. Of the 12 patients with recurrent attacks, all of whom had murmurs prior to therapy, a decrease in intensity of cardiac murmurs during therapy occurred in only 2 cases. An abnormal prolongation of the P-R interval was observed in 7 patients initially and developed during therapy in two additional patients. In 5 patients this finding had disappeared within 30 days after beginning medication whereas it persisted in 4 patients during the entire period of treatment. In 4 additional patients there was inversion of T waves either in the first or second limb leads or in several precordial leads. This abnormality disappeared in 3 instances during therapy but in 1 case with pancarditis, persisted during 2½ months of continued therapy during which high plasma salicylate levels were maintained.

Anemia, when present at the time of entry, disappeared in every instance during therapy. Leukocytosis observed initially in 17 patients, disappeared in 15 cases within 2 weeks while in 2 other patients it persisted throughout treatment. The corrected sedimentation rate (Wintrobe method) which was elevated in 17 patients, fell to normal in only 5 instances within 4 weeks after drug treatment was begun.

In 1 patient with an initial attack and in 5 patients with recurrent attacks, evidence of active rheumatic infection returned within 5 days after discontinuing therapy which had been maintained for 4 to 9 weeks. These patients, again, were given large doses of salicylates for a prolonged period with apparent improvement.

The follow-up period on these 18 patients has not been adequate to permit satisfactory evaluation of the results. One patient with an initial attack and 3 with recurrent attacks failed to return for study after leaving the hospital. One patient with recurrent rheumatic fever died on the

8th day of therapy. Another patient with recurrent acute rheumatic fever had an immediate recurrence of active infection after stopping salicylate medication on the 59th day of treatment. This patient died of salicylate intoxication 38 days after therapy was resumed.

The remaining 12 patients have been followed for periods of 2 to 20 months after termination of treatment. Nine have remained free from evidence of active infection. One additional patient in whom a good therapeutic response was obtained, developed another attack following a new respiratory infection which occurred 3 months after stopping medication. In 2 patients with recurrent rheumatic fever, both of whom had been given a second course of salicylate medication because of immediate recurrence following the first course, evidence of active rheumatic infection returned after the second course and persisted for many months thereafter.

The therapeutic response to large doses of salicylates in two adult cases of active rheumatic fever is described below.

Case Histories. CASE 1. O. T., a white male, 23 years of age, entered the hospital with an initial rheumatic attack of 4 days duration. This was characterized by the findings of fever, pharyngitis, arthritis, anemia, leukocytosis and an elevated sedimentation rate. The only abnormal electrocardiographic finding was an inverted T wave in Lead 4F.

The patient received 7.2 gm. (0.11 gm. per kg.) of sodium salicylate orally for 6 days. The daily oral dose was then increased to 12 gm. (0.18 gm. per kg.) and maintained at this amount for 31 days. There was rapid improvement with disappearance of clinical evidence of rheumatic activity. A systolic murmur which was noted over the apex of the heart during the second week of therapy, diminished in intensity during continued medication. An electrocardiogram taken 3 weeks after initiation of treatment was normal. The sedimentation rate and leukocyte count returned to normal values within 3 weeks. The volume of packed red cells was 33.5 cc. % on admission and 6 weeks later had risen to 45 cc. %. This patient has been followed for 18 months

and has remained symptom free. The apical systolic murmur is no longer audible.

CASE 2. B. K., a white female, 22 years of age, entered the hospital because of migratory arthritis of 3½ months duration. There had been no previous attack. In the preceding 10 weeks, she had been hospitalized elsewhere and had received sodium salicylate in variable doses, sulfonamides and finally 2,000,000 units of penicillin. The patient had continued to have fever and swelling of joints and had had several episodes of severe precordial pain.

At the time of admission to our hospital, the pertinent findings included fever, swollen tender joints and an increased sedimentation rate. An electrocardiogram showed sharply inverted T waves in the precordial Leads V₁ and V₂.

The patient's oral salicylate dose was rapidly raised to 12.6 gm. (0.22 gm. per kg.) per day (Fig. 1, Case C). The plasma salicylate level was maintained between 350 and 450 µg. per cc. There was prompt symptomatic improvement. The sedimentation rate fell to a normal value after 6 weeks of treatment. The initial electrocardiographic changes disappeared by the 32d hospital day. On the 49th day, the patient acquired mumps and the sedimentation rate again became elevated. Salicylate medication was discontinued 5 days later. In the 4 months subsequent to treatment, this patient has shown no clinical evidence of rheumatic activity.

**Clinical Material and Results. PEDI-
ATRIC GROUP.** Nine children, whose ages ranged from 9 to 15 years, received massive salicylate medication. Five were considered to be experiencing initial attacks. One of the 4 children with a history of previous rheumatic attacks, presented no clinical evidence of an active infection but was given large doses of salicylates in order to study the variations in plasma salicylate levels which may occur when constant dosage is maintained.

Arthritic manifestations were present in 4 of the 5 with initial attacks at the time salicylate therapy was instituted. All 5 had tachycardia and two showed electrocardiographic changes compatible with myocardial involvement. Four of this group were found to have moderately loud

apical systolic murmurs. Fever was present in two at the time of admission.

Two of the 3 patients with recurrent acute rheumatic attacks had joint symptoms. In addition, tachycardia and electrocardiographic changes were present but there were no murmurs or evidence of cardiac enlargement. In the 3d case, there was evidence of aortic and mitral valvular insufficiency. Fever was observed in only 1 of this group.

Laboratory studies revealed an anemia in 2 cases (volume of packed red cells 32 to 36 cc. %). Moderate leukocytosis was present in 4. The corrected sedimentation rate (Wintrobe) was elevated in 8 children with rheumatic activity.

Massive salicylate therapy was started within 10 days after the onset of rheumatic manifestations in 5 cases but rheumatic symptoms had been present at least 1 month in the remaining 3. Sodium salicylate was administered intravenously in doses of 0.10 to 0.33 gm. per kg. in 7 cases and orally in the 8th in a total daily dose of 0.22 gm. per kg. Intravenous medication was discontinued after 1 to 4 days and the same dosage was given orally in divided doses, every 4 hours day and night. With each oral salicylate dose, sodium bicarbonate in an amount ranging from 50 to 100% of the salicylate dose, was administered simultaneously. Enteric coated sodium salicylate tablets were not employed.

Symptomatic relief was obtained within 2 to 7 days. In 1 case the joint manifestations recurred on the 7th day after discontinuation of medication. Cardiac murmurs of great intensity, which were initially present in 3 instances, persisted without regression throughout and subsequent to salicylate therapy. The slight or moderate murmurs disappeared in 3 patients in whom they were present. Cardiac enlargement did not decrease in the 3 in whom it was demonstrated prior to the institution of salicylate therapy. Tachycardia persisted 7 to 10 days except in 1 patient in whom it persisted for many months.

The anemia, which was present in 2

patients at the time of entry, persisted throughout the period of salicylate medication. Leukocytosis continued in 2 and disappeared in 2 within 2 weeks after beginning treatment. The erythrocyte sedimentation rate returned to normal within 18 days in only 3 instances. In 2, it remained elevated for 2 months after salicylate therapy was begun.

There has been a period of 2 to 12 months since the discontinuation of salicylates in these patients. One of the 5 treated during an initial attack still has evidence of rheumatic activity and presents clinical signs of mitral valvular insufficiency. The 3 patients with recurrent acute rheumatic attacks are making satisfactory physical progress and are apparently free from rheumatic activity. Those without apparent rheumatic activity are being maintained on sulfanilamide prophylactically.

The response to salicylate therapy in 1 child with acute rheumatic fever is presented below in the form of a case abstract.

Case History. CASE 9. J. F., a 14 year old white boy entered the hospital because of malaise and migratory polyarthritides of 9 days duration. There was no past history of rheumatic episodes. Systolic murmurs were present over the apex and pulmonary area. There was swelling, redness and heat of the right knee. His blood showed a slight leukocytosis and an increased sedimentation rate. An electrocardiogram disclosed a prolonged P-R interval. There was no roentgenographic evidence of cardiac enlargement.

Sodium salicylate was administered intravenously for 2 days and then orally for 29 days in doses ranging from 0.13 to 0.17 gm. per kg. The plasma salicylate levels ranged from 330 to 412 μ g. per cc. The sedimentation rate became normal by the 19th day while other evidences of active infection disappeared more rapidly. One week after sodium salicylate was discontinued, there was a recurrence of joint pain and swelling. The sedimentation rate increased and the P-R interval became prolonged again. On the 5th day after recurrence, salicylate therapy was resumed and maintained for 75 days. The plasma salicylate levels varied between 300 and 400 μ g. per cc. The symp-

toms rapidly subsided. The sedimentation rate returned to a normal range on the 27th day. Six months later, the patient showed no evidence of rheumatic activity or of residual cardiac damage. He had made satisfactory physical progress, gaining 17 units on the Wetzel Grid²⁰ since his admission to the hospital. He had continued in the B-1 channel.

Salicylate Levels of the Plasma. In 19 patients with acute rheumatic fever and in 6 patients with other diseases, 6 to 30 plasma salicylate levels (average of 11 per person) were determined during the course of oral salicylate therapy. Other cases in which only a few levels were obtained, are not included in the discussion below. The plasma salicylate levels were determined according to a slight modification of the method of Brodie, Udenfriend and Co-

necessary to maintain the plasma levels in the range of 300 to 400 $\mu\text{g.}$ per cc. The range of dosage and the average dosage needed to obtain such levels with various forms of administration and in various groups is tabulated below (Table 1). The doses below (expressed in gm. per kg. of body weight) are the maximal doses needed in any given individual to obtain suitable levels. Often smaller doses produce satisfactory levels early in therapy and subsequently the dosage must be increased if high plasma salicylate levels are to be maintained.

The accompanying table clearly indicates that with both enteric coated sodium salicylate tablets and non-enteric coated tablets, there is great individual variation in dose requirement to obtain high plasma salicylate levels. In adults who received

TABLE 1.—FACTORS INFLUENCING THE DAILY AMOUNT OF ORAL SODIUM SALICYLATE NECESSARY FOR MAINTAINING PLASMA SALICYLATE LEVELS ABOVE 350 $\mu\text{g.}$ PER CC.

Type of case	Number studied	Cardiac failure	Type of salicylate tablet	NaHCO ₃ (in amounts equal to salicylate dose)	Range of dosage (gm./kg.)	Average dosage
Adults with acute rheumatic fever	5	none	enteric coated	none	0.14-0.24	0.21
Adults with acute rheumatic fever	3	none	enteric coated	yes	0.26-0.30	0.29
Adults with acute rheumatic fever	5	yes	enteric coated	none	0.06-0.28	0.16
Adults with other diseases	6	none	enteric coated	none	0.11-0.15	0.12
Children with acute rheumatic fever	6	none	non-enteric coated	yes	0.11-0.31	0.25

burn.¹ The error with this method as evidenced from many duplicate determinations and from recovery of known amounts of salicylate added to plasma, does not exceed 5%. All values are expressed in terms of plasma salicylic acid.

With oral therapy, all drug was administered at 4-hour intervals throughout the day and night. In 16 adults (10 with acute rheumatic fever and 6 with other diseases), oral medication consisted only of enteric coated sodium salicylate tablets. In 3 other adults, equal amounts of sodium bicarbonate were administered simultaneously with the enteric coated salicylate tablets. In the 6 children, equal amounts of sodium bicarbonate and non-enteric coated sodium salicylate tablets were employed. With each type of administration, it was observed that individuals varied greatly in the amount of drug which was

only enteric coated sodium salicylate tablets, the average oral dose necessary to obtain high plasma salicylate levels appeared to be greater in the group with acute rheumatic fever without evidence of cardiac failure than in an equal number of patients in whom cardiac failure was present with the active infection. The small group of adults who received equal amounts of sodium bicarbonate with the enteric coated salicylate tablets, appeared to require slightly more salicylate than the group of patients with active infection but without cardiac failure, who received only the enteric coated tablets. Patients without rheumatic fever seemed to require less drug than those with this disease to obtain comparable plasma salicylate levels. The average oral dosage of salicylates in the children who received non-enteric coated sodium salicylate tablets and equal

amounts of sodium bicarbonate, did not differ markedly from the dose requirement in the adults with acute rheumatic fever who received enteric coated sodium salicylate tablets.

During oral administration of a constant dosage of sodium salicylate to patients with acute rheumatic fever, it is a frequent finding to observe a progressive rise in the plasma salicylate level during the first 2 weeks of medication. After this time, the level tends to drop. In 18 of the 26

periods. This finding in the patients with acute rheumatic fever suggests that they develop an increased rate of excretion or destruction of the drug during prolonged therapy. Less than 0.3 gm. of salicylate was present in a single 24-hour stool specimen of 2 adults who had been receiving 18 gm. of enteric coated sodium salicylate daily.

In spite of careful regulation of dosage, the plasma salicylate levels from day to day or week to week in a given individual

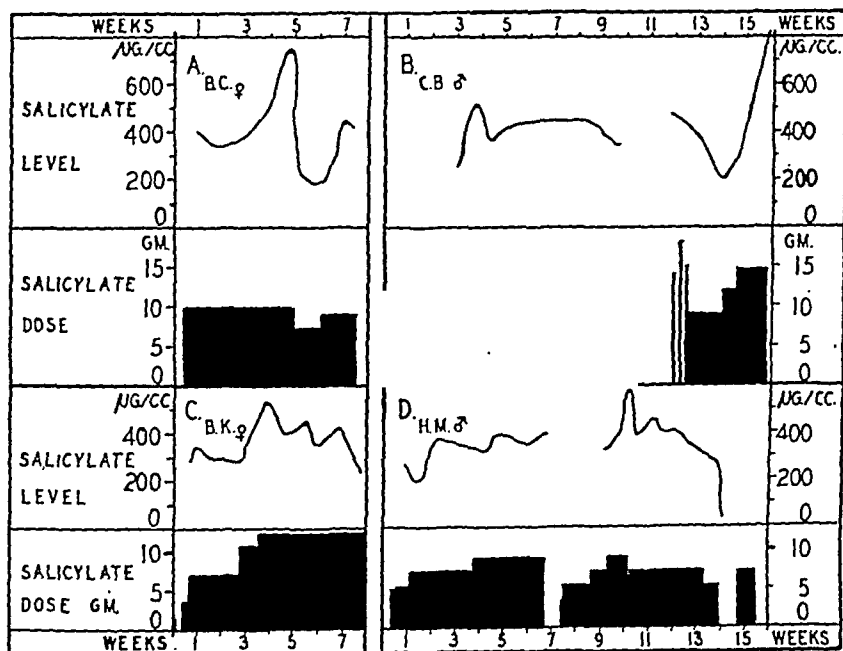


FIG. 1.—Relationship of plasma salicylate level to oral salicylate dosage in 4 patients.

Note in Cases B, C and D, the apparent reduction in plasma salicylate level which occurred on constant dosage and which necessitated increasing amounts of drug to maintain high plasma levels. Note, also, the unexplained rises in plasma salicylate levels on constant dosage in Case A and in Case B (during second period of drug therapy).

patients with acute rheumatic fever, it was necessary, after 2 or 3 weeks of medication, to increase by 10 to 50% the original salicylate dosage in order to maintain suitable levels (Fig. 1). In only 4 instances did the level continue to rise after the first 2 weeks of therapy when dosage was constant and here it was necessary to reduce the dosage slightly. No similar decline in level after 2 weeks of therapy on constant dosage was noted in 5 adults without acute rheumatic fever who received oral medication for prolonged

(both adults and children), often varied as much as 100 µg. per cc. on constant dosage. This makes it difficult to maintain the plasma salicylate level above 350 µg. per cc. at all times. If one strives to avoid this by maintaining an average plasma level of 450 µg. per cc. one brings the patient uncomfortably close to the toxic range.

In 4 patients, a total of 5 or 6 determinations of plasma salicylate were made at 3-hour intervals in a single day during continued oral therapy. The variation in plasma salicylate levels throughout the

day varied from 50 to 90 $\mu\text{g.}$ per cc. and the levels in each instance were higher in the morning than in the evening.

During oral salicylate therapy, while a constant dosage was being maintained, 2 adults (receiving enteric coated salicylate tablets) and 2 children (receiving non-enteric coated tablets) developed unexplained sudden increases in their plasma salicylate levels to values 200 to 300 $\mu\text{g.}$ per cc. above previous levels (Fig. 1). The high levels were accompanied by toxic manifestations. The unexplained rise in level could not be attributed to significant variation in fluid intake or output in these patients.

Our experience with plasma salicylate levels attainable after intravenous medication is limited. In 3 adults who received 10 gm. of sodium salicylate intravenously, the plasma salicylate levels at the end of the infusion ranged from 400 to 600 $\mu\text{g.}$ per cc. and 18 hours later they had fallen to levels varying from 250 to 350 $\mu\text{g.}$ In 3 patients with mild cardiac failure and in 2 patients without cardiac failure, 5 or 6 plasma salicylate levels were obtained at approximately 3-hour intervals over the period ranging from 1 to 18 hours after completing a single infusion. The rate of decline of levels after terminating the infusion was considerably slower in the 3 patients with cardiac failure than in the 2 without failure. In 1 patient who received single daily intravenous infusions of 15 gm. of sodium salicylate over a 3-hour period, the volume of the infusion was maintained at 500 cc. for 1 week and at 1500 cc. for the next week while the time for the infusion was constant. The plasma salicylate levels which were determined daily, 18 hours after the previous infusion ranged from 400 to 540 $\mu\text{g.}$ per cc. The observed fluctuations were not related to the volume of the infusion.

Salicylate Toxicity. A number of symptoms of salicylate toxicity have been observed in a total of 38 patients who have received large doses of this drug. This includes 27 patients with active rheumatic fever and 11 with other diseases. Therapy

was maintained for 4 to 16 weeks in 30 patients and a shorter period in the remaining 8. The plasma salicylate level was determined at least once during each week of salicylate medication and usually 2 to 3 times a week.

In general, the severity of the toxic symptoms in a given individual was greater when the plasma salicylate level was high. No serious intoxication appeared in any patient whose plasma salicylate level was less than 400 $\mu\text{g.}$ per cc. and often patients tolerated levels above 500 $\mu\text{g.}$ for prolonged periods without difficulty. The highest plasma salicylate values ranged from 600 to 800 $\mu\text{g.}$ per cc. in 6 cases, from 400 to 600 in 9 cases and from 200 to 400 in 13 cases.

Tinnitus which was usually accompanied by slight to moderate reduction in hearing was experienced by 34 of the 38 patients receiving salicylate therapy. In some instances, tinnitus did not appear until the plasma salicylate level exceeded 500 $\mu\text{g.}$ per cc. whereas in others, it was noted when the plasma levels were below 200. Usually the severity of tinnitus in a given patient increased with rising plasma salicylate levels. Deafness to a noticeable degree, which was present in only 5 patients, invariably disappeared within 2 to 3 days after medication was stopped while tinnitus often persisted several days longer.

In 2 adults receiving oral salicylate medication, audiometer studies were made weekly during therapy and daily for the first 4 days after its discontinuance. The plasma salicylate levels in these individuals varied from 220 to 440 and 300 to 550 $\mu\text{g.}$ per cc., respectively, during these studies. Reduction in hearing by air conduction below pretreatment values ranged from 20 to 35%. The more marked instances of loss of hearing seemed to occur when the plasma salicylate levels were highest. Following termination of medication, there was complete recovery of hearing in each patient in 3 to 4 days.

Nausea and vomiting which occurred in 25 of the patients receiving salicylate med-

ication, usually appeared early in therapy and later disappeared even though the salicylate dosage was subsequently increased and the plasma levels became higher. With very high plasma salicylate levels (above 500 $\mu\text{g. per cc.}$) nausea and vomiting were observed in 7 patients and disappeared when the dosage was reduced. These symptoms were likely to occur toward the end of the period of infusion in patients receiving intravenous medication.

During the course of prolonged salicylate therapy, an acne-form eruption appeared in 6 adult females and in 2 adult males. This usually became manifest during the 2d week and often persisted, although in one instance it disappeared during continued therapy.

Urinary changes during salicylate medication were infrequent. There was slight transient albuminuria in 4 of the 27 adults and one in the 11 children. In one severely intoxicated patient, albumin, red blood cells and granular casts appeared in the urine. It should be emphasized, however, that in at least 5 other patients with severe intoxication, no albuminuria occurred. Qualitative Benedict's tests on the urines frequently gave a trace to one plus reduction. In 4 adults and in 3 children, all of whom had plasma salicylate levels ranging from 400 to 600 $\mu\text{g. per cc.}$, there was acetonuria lasting from 4 days to 3 weeks. In all patients, acetonuria was accompanied by a reduction in the plasma carbon dioxide combining power.

Hyperventilation was observed during salicylate therapy in 22 of the 27 adults and in at least 5 of the 11 children. It usually did not appear until the plasma salicylate level was above 400 $\mu\text{g. per cc.}$ It was observed frequently in the period immediately following an intravenous infusion.

In all patients, careful search for a hemorrhagic tendency was made. In 14 patients, plasma prothrombin times were determined at least once a week and sometimes daily. The method of Quick¹⁵ was used. It has been reported that sodium salicylate and other salicylate derivatives

lengthen the prothrombin time.^{7,13,16} We likewise have observed this change in patients receiving salicylates. This will be reported in detail elsewhere.² It deserves mention, however, that in spite of significant prolongation of the prothrombin time, hemorrhagic manifestations were observed in only one instance. This case was summarized below. In one patient of 5 in whom frequent tourniquet tests (Rumpel-Leede) were made during therapy, the test became positive for 4 days and then again became negative in spite of continued salicylate administration with maintenance of high plasma levels. In the other patients, the tourniquet test was negative.

No evidence of marked liver damage could be demonstrated in any patient during salicylate therapy. The icterus index, which was determined many times in each case, did not become elevated. The bromsulphalein test performed in 3 patients and the hippuric acid test in 1 patient during salicylate therapy, gave normal results. However, the cephalin flocculation test became positive in the 6 adults in whom this test was performed during therapy. These patients had plasma salicylate levels above 400 $\mu\text{g. per cc.}$ The *in vitro* addition of sodium salicylate to serum from normal controls, failed to give a positive test.

Evidence of central nervous system disturbance was observed in a few patients, all of whom had plasma salicylate levels above 500 $\mu\text{g. per cc.}$ This included hallucinations (5 cases), mental confusion (3 cases), vertigo (5 cases), diplopia (2 cases), "pounding of the head" (1 case), coarse tremor of hands (1 case) and coma (6 cases). Drowsiness and moderate euphoria were common manifestations at high plasma levels but were difficult to appraise.

Random determinations of plasma carbon dioxide combining power in 17 patients, demonstrated reductions to values ranging from 28 to 45 volumes % in 14 cases. No significant reduction occurred in any patient whose plasma salicylate level was below 400 $\mu\text{g. per cc.}$ and the greatest reductions in the same patient and in the

entire group correlated roughly with the highest plasma salicylate values. The pH of venous blood (glass electrode method) performed in 2 patients with high plasma salicylate levels with reductions of their plasma carbon dioxide combining power below 40 volumes % but without acetoneuria, were found to be normal.

A small number of determinations of blood urea nitrogen, plasma creatinine and plasma chloride revealed occasional slight rises which were inconstant in the same individual during therapy and inconstant for the group.

The corrected sedimentation rate showed surprising variation in its behaviour during massive salicylate therapy. In the adult group, the sedimentation rate returned to normal values in only 11 of the 18 patients with rheumatic fever after prolonged therapy, while in the 8 children, it ultimately returned to a normal range in every instance. In both adults and children it often took 5 to 8 weeks of continued medication before any significant reduction in the sedimentation rate was observed. More striking was the observation that, in the first 2 to 4 weeks after instituting salicylate medication, an increase in the sedimentation rate above the pretreatment levels occurred in approximately two-thirds of the patients. This rise was often marked and persisted usually less than 2 weeks but occasionally the sedimentation rate remained higher than the pretreatment levels for as long as 4 to 5 weeks of continued therapy. In 2 adults, this elevation persisted during many weeks of therapy and promptly fell to normal when therapy was stopped. Moreover in the instances where the sedimentation rate rose during the early period of therapy, it often afforded a striking contrast to the leukocyte count and other evidences of active rheumatic infection which were diminishing at this time. This suggested the possibility that the medication itself, might be influencing the sedimentation rate. In 4 of 5 adults with diseases other than rheumatic fever, a rise in the sedimentation rate likewise occurred after in-

itiating salicylate therapy and, in 2 instances, return to pretreatment levels did not occur until therapy was discontinued.

If anemia be excluded, an elevation of the plasma fibrinogen is the most significant factor in producing an elevated sedimentation rate.^{6,9,14} An increase in plasma globulin or lipid may also produce elevation of the sedimentation rate.^{6,9} Other investigators^{5,9} have demonstrated the correlation between plasma fibrinogen level and corrected sedimentation rate in cases of acute rheumatic fever. One of us (V. J., in conjunction with F. W. Clausen) has made multiple fibrinogen determinations in 5 adults with acute rheumatic fever prior to, during and following the course of salicylate therapy (Figs. 2 and 3). While there was no linear correlation, in every instance where the sedimentation rate (corrected or uncorrected for anemia) was increased, the plasma fibrinogen was elevated. Elsewhere one of us³ has reported a similar rise in plasma fibrinogen and in sedimentation rates in control subjects with initially normal sedimentation rates and in rabbits that were receiving massive salicylate therapy. In many instances, the sedimentation rate and the plasma fibrinogen ultimately fall to normal values after the initial increase in spite of continued therapy and maintained high plasma salicylate levels.

Following discontinuation of therapy, a moderate increase in the sedimentation rate was observed in approximately half of the patients with rheumatic fever in whom the values had been normal prior to the discontinuance of medication. This rise usually appeared within 3 to 4 days, persisted 1 to 4 weeks and seldom was attended by other evidence of active infection. A similar type of response was noted after stopping treatment in cases of rheumatic fever by Ernstene⁵ who used small doses of salicylates and by Coburn⁴ who used massive doses.

The possibility that there is an increase in plasma volume during salicylate therapy was afforded by the finding of a marked drop in the volume of packed red cells

which occurred in 13 of 18 adults and in 2 of 9 children during treatment. This drop which ranged from 3 to 8% of the total packed cell volume, usually appeared within the first few days of treatment. With continued therapy, the hematocrit reading often returned to its original level or if anemia had been present, rose above the original value. In those patients exhibiting severe salicylate intoxication, a further drop in the volume of packed red

Case Histories. C. B. A 41 year old white, who had had repeated admissions to the hospital because of recurrent rheumatic attacks, pulmonary infections and mild congestive heart failure, was readmitted because of tender swollen joints of 10 days duration. On examination, the patient was found to have acute polyarthrititis, mitral stenosis and insufficiency, auricular fibrillation and mild cardiac decompensation. There was moderate leukocytosis and an elevated sedimentation rate.

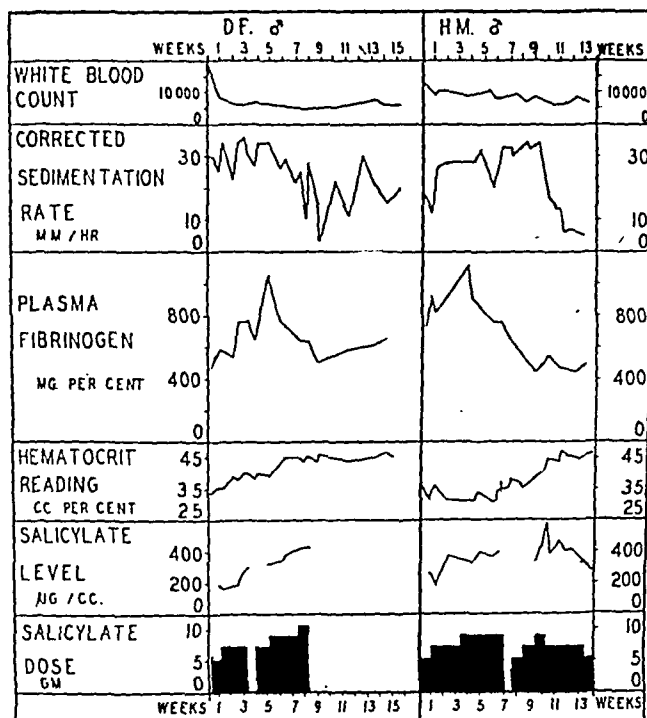


FIG. 2.—Changes observed in plasma fibrinogen, leukocyte count, sedimentation rate and hematocrit reading in 2 patients receiving large doses of sodium salicylate orally.

In Case D. F., observe the rise in fibrinogen and the rapid disappearance of anemia and leukocytosis during the first 6 weeks of therapy. In Case H. M., note again the initial increase in plasma fibrinogen with a subsequent decrease as well as the changes in the sedimentation rate and hematocrit reading.

cells occurred at such a time. Preliminary measurements by a dye method in several rabbits and in several persons receiving salicylate therapy also indicate that there is an increase in plasma volume during salicylate administration. Obviously, an increased plasma volume would be an unfavorable complication in a person with impaired cardiac function.

The salient features of 2 cases exhibiting severe salicylate intoxication are presented below.

The patient was digitalized and salicylate medication was begun (Fig. 1, Case B). For 71 consecutive days, he received equal quantities of sodium bicarbonate and sodium salicylate in maximal daily oral dosage of 18 gm. (0.29 gm. per kg.) of each. There was symptomatic improvement. However, on the 71st day, he suddenly developed pulmonary edema. Salicylate medication was discontinued for 1 week and then resumed. The day following cessation of medication, the joints again became swollen and tender. With renewed therapy, he received first 9

(0.14 gm. per kg.) and later 14.4 gm. (0.23 gm. per kg.) of sodium salicylate daily without added sodium bicarbonate. The plasma salicylate level 21 days after resumption of therapy was 432 μ g. per cc. The volume of packed red cells was 46 cc. % at this time. Six days later, with the same dosage, the salicylate level of the plasma was found to be 812 μ g. per cc. The patient was comatose and there was severe pulmonary congestion. Medication was discontinued. The previous

104.4° F. Clinically there was no evidence of a hemorrhagic tendency. Death appeared to have resulted from pulmonary edema.

Autopsy. Petechial hemorrhages were present in the epicardium and in the serosa of the small intestine. The brain appeared edematous and, on cut section, numerous petechial hemorrhages were present in the white substance. The heart was enlarged, weighing 700 gm. There was marked calcific stenosis of the mitral valve. Histo-

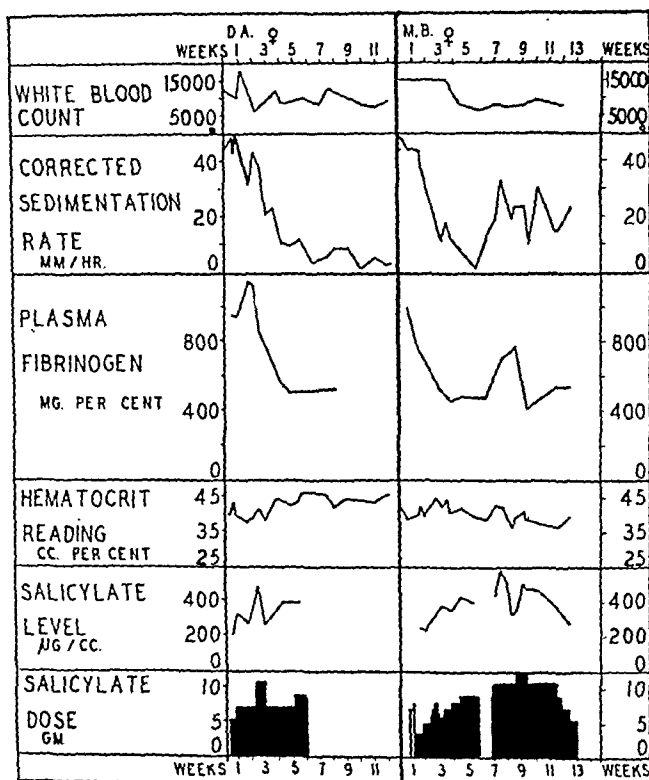


FIG. 3.—Changes observed in plasma fibrinogen, leukocyte count, sedimentation rate and hematocrit in 2 patients receiving large doses of sodium salicylate orally.

In Case D. A., note the changes in plasma fibrinogen and sedimentation rate during salicylate therapy. In Case M. B., observe the rise in plasma fibrinogen which occurred with readministration of the drug. Note also the fluctuations in plasma level as compared to variations in drug dosage.

day, the patient had been drowsy, had been hyperventilating and had complained of severe tinnitus and blurring of vision. With the high plasma salicylate level, the volume of packed red cells fell to 35 cc. % and the plasma prothrombin time became greatly prolonged. In spite of all supportive measures, the patient died 18 hours later. During the terminal period of coma, there was persistent marked cyanosis which was not relieved by the intratracheal administration of oxygen. Terminally the temperature rose to

logically the heart muscle contained many small foci of lymphocytes and histiocytes without characteristic Aschoff bodies. The lungs were congested and edematous. One small subpleural infarct was present. No significant gross or histologic abnormalities were observed in the aorta, kidneys, spleen, liver, adrenals, pancreas or striated muscle.

COMMENT. The petechial hemorrhages demonstrated in the brain, could have resulted from the prolonged period of

anoxia. A hemorrhagic diathesis, if it existed, was scarcely a significant factor in the fatal outcome. Death appeared to have resulted from pulmonary edema.

Case History. T. B. A 39 year old male moron with secondary syphilis was given sodium salicylate intravenously for 3 consecutive days to determine the effect of this drug on the prothrombin level. Prior to medication he was asymptomatic. On the first day he received 20 gm. of this drug (0.38 gm. per kg.) in 1000 cc. of saline. There was nausea and tinnitus following the injection. The next day (18 hours later) the plasma salicylate level was 336 μ g. per cc. He was now given 15 gm. (0.29 gm. per kg.) of the drug. Nausea, vomiting and deafness appeared immediately after this injection and persisted for several hours. The 3d day, the plasma salicylate level prior to injection was 616 μ g. per cc. He was given 10 gm. (0.19 gm. per kg.) of sodium salicylate. A few hours later he became delirious, developed marked dyspnea and bleeding from the nose and gums. He vomited frequently. The following morning, 18 hours after the last of the 3 injections, the plasma salicylate level was 564 μ g. per cc. The patient was now comatose, dyspneic and cyanotic. There was pulsus alternans. Loud rhonchi were present in the chest. The 2d day after termination of medication, the patient was still stuporous and moderately cyanotic. The plasma salicylate level on this day was 318 μ g. per cc. Bleeding from the nose and gums had ceased. The following day, he was less stuporous but was irrational and the speech was slurred. On the 4th day after the last salicylate injection, slight cyanosis was still present. Speech continued to be slurred. There were visual hallucinations. An inconstant divergent strabismus was noted. The patient recovered completely in the 2 subsequent days.

During the salicylate intoxication, interesting laboratory changes were observed. The volume of packed red cells, initially

42 cc. %, fell to 34 cc. % following the third injection and did not rise appreciably over 5 subsequent days and did not attain its original level for 3 more days. There was no rise in the icterus index. The prothrombin content of the plasma fell to 20% of the normal value on the 3d day of medication. The patient received 60 mg. of vitamin K intravenously at this time and 24 hours later, the prothrombin time was normal. The day following the last dose of salicylate, the carbon dioxide combining power of the plasma was 28 volumes % and 5 days later, it had returned to a normal value. At the peak of intoxication, the urine contained acetone, albumin and many granular casts. These changes disappeared during the 4 subsequent days. An electrocardiogram prior to therapy was normal. One taken 2 days after termination of medication showed depression of ST segments and lowering of T waves in the 3 standard limb leads. Serial precordial leads showed flattening and partial inversion of T waves. A tracing on the following day showed similar changes. However, the QT interval was now prolonged, being 0.52 second with a cardiac rate of 65. The expected QT for this rate is 0.35 to 0.45 second. Two days later, the QT interval was 0.42 second, the rate was 75 and T waves in the standard limb leads were flat. A few days later there were no electrocardiographic abnormalities.

Conclusions. Treatment with large doses of salicylates appeared to be effective in the 5 patients with initial attacks and in 4 of the 7 patients with recurrent attacks who could be followed for short periods after medication had been stopped. It is probable that the results would not appear so favorable if every patient could have been followed. Several of those who did not return for examination, had evidence suggestive of persistent rheumatic activity at the time of discharge from the hospital.

REFERENCES

1. BRODIE, B. B., UDENFRIEND, S., and COBURN, A. F.: *J. Pharm. and Exp. Therap.*, **80**, 114, 1944.
2. CLAUSEN, F. W., and JAGER, B. V.: Unpublished data.
3. CLAUSEN, F. W., and JAGER, B. V.: *Proc. Soc. Exp. Biol. and Med.* (to be published).
4. COBURN, A. F.: *Bull. Johns Hopkins Hosp.*, **73**, 435, 1943.
5. ERNSTEINE, A. C.: *Am. J. Med. Sci.*, **180**, 12, 1930.
6. FAHRAEUS, R.: *Physiol. Rev.*, **9**, 241, 1929.
7. FASHENA, G. J., and WALKER, J. N.: *Am. J. Dis. Child.*, **68**, 369, 1944.

8. GRIFFITH, G. C., LEAKE, W. H., and BUTT, H.: Modern Concepts of Cardiovascular Disease, 14, No. 6, 1945.
9. HAM, T. H., and CURTIS, F. C.: Medicine, 17, 447, 1938.
10. HARTMAN, A. F.: J. Pediat., 26, 214, 1945.
11. HOPKINS, P.: Lancet, 1, 145, 1945.
12. LAWSON, R. B.: North Carolina Med. J., 5, 477, 1944.
13. MEYER, O. O., and HOWARD, B.: Proc. Soc. Exp. Biol. and Med., 53, 234, 1943.
14. OAKLEY, W.: Lancet, 1, 312, 1938.
15. QUICK, A. J.: Am. J. Physiol., 118, 260, 1937.
16. SHAPIRO, S.: J. Am. Med. Assn., 125, 546, 1944.
17. SMULL, K., WEGRIA, R., and LELAND, J.: J. Am. Med. Assn., 125, 1173, 1944.
18. TROLL, M. M., and MENTEN, M. L.: Am. J. Dis. Child., 69, 37, 1945.
19. WEGRIA, R., and SMULL, K.: J. Pediat., 26, 211, 1945.
20. WETZEL, N. C.: J. Pediat., 22, 82, 1943.

EFFECT OF SODIUM BICARBONATE ON THE THERAPEUTIC EFFECTIVENESS OF SULFADIAZINE IN MICE

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ADMINISTRATION of sodium bicarbonate to rats fed sulfadiazine-containing diets has been shown to result in a marked depression of the sulfadiazine blood level.⁸ Clinical studies¹⁰ have also indicated some depression of blood level and increased urinary excretion of sulfadiazine after the oral administration of sodium bicarbonate. Since sodium bicarbonate has been shown to be effective clinically^{4,5,6} and experimentally^{7,8} in the prevention or correction of sulfadiazine-induced renal lesions, it became of interest to determine how sodium bicarbonate might affect the therapeutic activity of sulfadiazine.

Experimental. Purified diets were prepared in which sulfadiazine (0.1 to 0.5%) or sodium bicarbonate (0.3 to 4%) and sulfadiazine replaced equal weights of sucrose in the basal diet.* Female albino mice (N.I.H. strain) raised on Purina chow and weighing 17 to 22 gm. were fed one of the experimental diets. Groups of approximately 20 mice were used and 5 or more groups were compared in each experiment. The test organism was a virulent strain of Type 1 pneumococcus. When passed through mice every week or more often, this strain has maintained a virulence such that 0.5 cc. of a 6-hour culture in dextrose, veal-infusion broth at a dilution of 10^{-8} is uniformly lethal to mice when inoculated intraperitoneally. After the mice had been fed one of the experimental diets for 5 days, they were inoculated intraperitoneally with a 0.5 cc. of a 10^{-6} dilution of the culture containing approximately 500 organisms.† Inoculations were made in rotation, taking 1 mouse from each group under

test. The mice were observed for a period of 2 weeks.

The data in Figure 1 indicate the mortality of mice fed diets containing varying amounts of sulfadiazine with and without sodium bicarbonate. The mortality was significantly greater among mice fed the diets containing 4% sodium bicarbonate. Thus the mortality was only 6% when mice were fed a 0.4% sulfadiazine-containing diet without sodium bicarbonate while it was 48% when sodium bicarbonate (4%) was incorporated in the diet. When administered in smaller amounts, the effects of sodium bicarbonate were less marked.

In order to determine the mechanism of action of sodium bicarbonate in increasing mortality, determinations were made of sulfadiazine intake (as calculated from food intake), absorption and blood concentration. Mice were fed a 0.3% sulfadiazine-containing diet (No. 1020) or a diet (No. 1032) containing 0.3% sulfadiazine and 4% sodium bicarbonate. Each diet was fed to 36 mice divided into 12 groups (cages) of 3. The average, daily food intake determined over a 4-day period was 7.8 gm. (range: 5.5 to 9.9) per 3 mice on diet No. 1020 and was also 7.8 gm. (range: 5 to 11.6) per 3 mice on diet No. 1032. Determination of the sulfadiazine content of feces collected during the 4 day period indicated that an average of 2.1% (range: 1.3 to 2.5) of the ingested sulfadiazine was unabsorbed in mice fed diet No. 1020 and 2.3% (range: 1 to 4) in mice fed diet No. 1032. Blood concentrations of sulfadiazine (free)‡ were determined by the Bratton and Marshall method² on blood samples obtained by decapitation and pooled for each group of 3 mice. As indicated in Figure 1, the average

* The basal diet (No. 1029) consisted of casein (Smaco) 18%, Crisco 8%, salt mixture No. 550³ 4%, corn oil (containing 8000 units of vitamin A and 800 units of vitamin D [Natola] per gram) 2%, ethyl laurate (containing 100 mg. of α -tocopherol per gram) 0.12%, and cerelese 67.88%. Into 100 gm. of this diet were incorporated 1 mg. of thiamine hydrochloride, 1 mg. of pyridoxine hydrochloride, 4 mg. of calcium pantothenate, 2 mg. of niacin, 200 mg. of choline chloride, 0.001 mg. of biotin and 0.4 mg. of 2-methyl-1,4-naphthoquinone.

† We are indebted to Dr. Josephine M. Junge for providing the bacterial cultures used in these studies.

‡ Determination of "total" sulfadiazine revealed only traces or no detectable amounts of "conjugated" sulfadiazine.

blood sulfadiazine concentration was 13.2 mg. % (range: 10.3 to 17.3) for mice fed the 0.3% sulfadiazine-containing diet (No. 1020) and 7.1 mg. % (range: 6 to 8.5) for mice fed the 0.3% sulfadiazine, 4% sodium bicarbonate-containing diet (No. 1032). The average blood sulfadiazine concentration for 5 groups of 3 mice fed diet No. 1064 containing 0.5% sulfadiazine and 4% sodium bicarbonate was 10.7 mg. % (range: 9.2 to 12).

the result of increased renal clearance of sulfadiazine in the presence of sodium bicarbonate.

Of interest in relation to the present findings are the studies of Marshall and Litchfield,⁹ and Rosenthal.¹¹ The former⁹ found that sulfanilamide was more toxic to fasting mice than to fed mice and that this difference was related to the blood

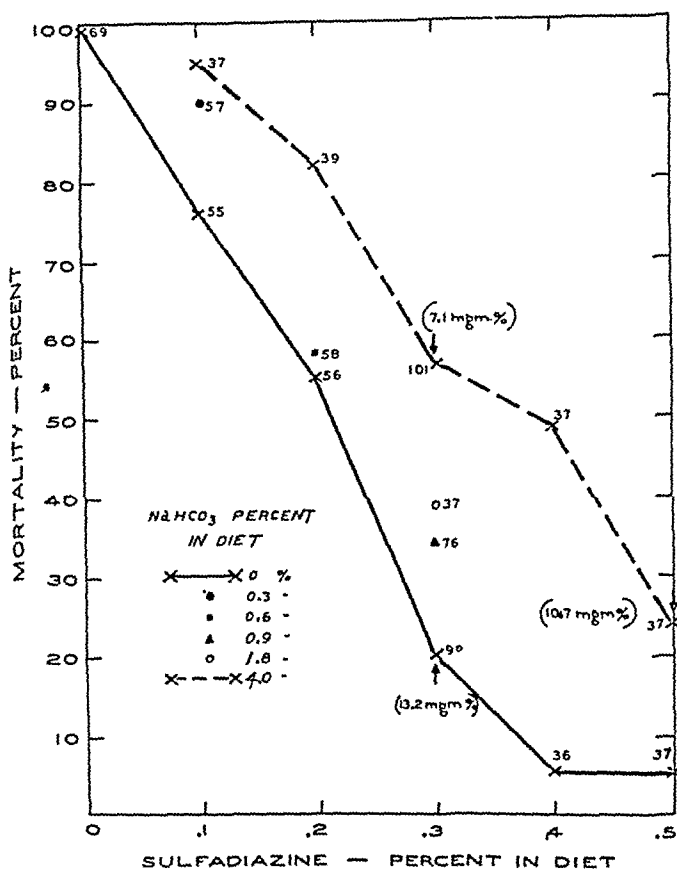


FIG. 1.—Mortality of mice inoculated with pneumococci and fed sulfadiazine-containing diets with and without sodium bicarbonate. The number at each point in the figure indicates the number of mice used to determine the % mortality at that point. The numbers in parentheses indicate blood sulfadiazine concentrations (see text).

Discussion. The inclusion of sodium bicarbonate in the diet has been found to impair the therapeutic effectiveness of sulfadiazine in mice. This sodium bicarbonate effect was not associated with any decrease in the intake or absorption of sulfadiazine but rather appeared to be related to a reduction of the blood concentration of sulfadiazine. The work of Beyer *et al.*,¹ and Earle³ suggests that the depression of sulfadiazine blood levels is

sulfanilamide concentrations. Rosenthal¹¹ showed that sulfanilamide was therapeutically more effective in mice on a low protein diet than in mice fed diets of higher protein content. Higher blood sulfanilamide concentrations were observed in the mice fed the low protein diet.

It is important to note that although sodium bicarbonate at dietary levels under 2% seemed to impair sulfadiazine therapeutic action, the most significant effects

were obtained with a level of 4% in the diet. This level of sodium bicarbonate represents approximately 10 times the weight of sulfadiazine when fed at a therapeutically effective level. For clinical use, Gilligan *et al.*⁵ have recommended a sodium bicarbonate dose for adults of 18 gm. daily or approximately 3 times the weight of the usually accepted dose of sulfadiazine.

Clinical studies^{4,5,6} and experimental work^{7,8} have indicated the effectiveness of sodium bicarbonate in the prevention or correction of sulfadiazine renal lesions. We were able to show in rats⁸ that severe renal lesions could be uniformly produced by sulfadiazine at a 1% level in the diet. These severe lesions were regularly prevented by sodium bicarbonate even when high blood sulfadiazine concentrations resulted from raising the dietary level of

sulfadiazine to 4%. It would appear desirable to use sodium bicarbonate for the prevention of renal lesions but to give close attention to the maintenance of therapeutically effective blood levels of sulfadiazine during the administration of sodium bicarbonate.

Summary. Sodium bicarbonate in large amounts markedly depressed the blood concentrations and the therapeutic effectiveness of sulfadiazine in mice inoculated with pneumococci. These effects could be overcome by raising the dosage of sulfadiazine.

It is suggested that sodium bicarbonate be used to prevent renal lesions and that close attention be given to the maintenance of therapeutically effective blood levels of sulfadiazine.

REFERENCES

1. BEYER, K. H., PETERS, L., PATCH, E. A., and RUSSO, H. F.: *J. Pharmacol.*, **82**, 239, 1945.
2. BRATTON, A. C., and MARSHALL, E. K., JR.: *J. Biol. Chem.*, **128**, 537, 1939.
3. EARLE, D. P., JR.: *J. Clin. Invest.*, **23**, 914, 1944.
4. FOX, C. L., JR., JENSEN, O. J., JR., and MUDGE, G. H.: *J. Am. Med. Assn.*, **121**, 1147, 1943.
5. GILLIGAN, D. R., GARB, S., WHEELER, C., and PLUMMER, N.: *J. Am. Med. Assn.*, **122**, 1160, 1943.
6. JENSEN, O. J., JR., and FOX, C. L., JR.: *J. Urol.*, **52**, 346, 1944.
7. JENSEN, O. J., JR.: *AM. J. MED. SCI.*, **206**, 746, 1943.
8. KORNBERG, A., ENDICOTT, K. M., DAFT, F. S., and SEBRELL, W. H.: *Pub. Health Rep.*, **60**, 661, 1945.
9. MARSHALL, E. K., JR., and LITCHFIELD, J. T.: *J. Pharm. and Exp. Ther.*, **67**, 454, 1939.
10. PETERSON, O. L., GOODWIN, R. A., JR., and FINLAND, M.: *J. Clin. Invest.*, **22**, 659, 1943.
11. ROSENTHAL, S. M.: *Pub. Health Rep.*, **56**, 1880, 1941.

PENICILLIN IN ACUTE NEPHRITIS IN CHILDREN

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FOLLOWING the experiments and research which have shown the antibacterial action of penicillin against a wide variety of pathogenic organisms, its use has now been extended to include a large number of different clinical diseases in man.

Acute nephritis is, in the majority of cases, secondary to some infective process. It has already been suggested that penicillin therapy is theoretically indicated in this condition, but we do not know of any report of a series of cases so treated.

In this small series of cases every patient was in a desperate condition, either due to neglect or due to repeated exacerbations within a short period in an anemic and devitalized child or the indiscriminate use of "sulfa" drugs based purely on blood counts showing a variable amount of leukocytosis. Even against these odds penicillin therapy carefully carried out has given extraordinarily encouraging results.

The essential feature of the disease being the recurrent nature of renal inflammation secondary to another infective focus, one postulates that if the primary focus can be eliminated the kidneys have a better chance of recovery and of remaining free from repeated attacks and consequent progressive degeneration. This primary infective focus, we know, is to be found in the nasopharynx, respiratory system or elsewhere. It is very often due to a hemolytic streptococcus, admittedly a highly susceptible organism to the "sulfa" group of drugs; but the kidneys do not tolerate this group well and the use of any form of intensive "sulfa" therapy in acute nephritis is fraught with grave dangers of toxic complications.

Evidence of renal toxicity has never been reported by workers who have used penicillin in the treatment of various diseases. The fact of its being completely

devoid of toxic effects on the kidneys makes it increasingly imperative that a more extensive trial be given it in the treatment of acute nephritis, especially in those cases where an infective focus, demonstrable or otherwise, is the primary cause of the renal condition.

The absence of toxicity of penicillin for most other tissues is another great advantage in its use in acute nephritis. There is no toxic disturbance in the peripheral blood or in the hemopoietic system. Unlike the "sulfa" drugs, penicillin can be successfully used if there is severe anemia, marked leukopenia or even, as recorded, in the presence of agranulocytosis. I have seen in patients of pneumonia complicating typhoid, lowered leukocyte counts actually rise during or after penicillin therapy.

If pyrogen free penicillin is used, constitutional reactions such as fever, malaise, headache, etc., should not occur.

When the observations just mentioned are taken into account regarding the extremely low toxicity of penicillin, it becomes at once apparent that favorable results may be expected in its use in acute nephritis, a condition where the question of drug toxicity is one of utmost importance in view of impaired renal function. It is obvious that penicillin, or for that matter any other drug, can have no possible therapeutic effect on the damage already done to the renal cells. In those cases, however, where there is evidence of an active septic focus, acting as a strong bactericidal agent, it removes or eliminates the source of infection. Furthermore, it is conceivable that it removes the inflammatory congestion in the renal tissues, particularly the cellular exudate between the layers of Bowman's capsule and the exudative process all over the interstitial

TABLE 1.—ANALYSIS OF CASES

Case No.	Age	Sex	Days since onset	Daily range of temp. at start of treatment (° F.)	White cell total count (thous.)	Edema	Daily urine output at treatment (ounces)	Penicillin			Results	Ultimate results and comments
								Dosage (units, thous.)	Days treated	Total dosage (units, thous.)		
1	6 yrs.	F	12	102-104	12.7	Moderate	12	10, 4 hourly	3½	22.0	Satisfactory	Temp. came to nor. in 5 days but rose to 99° occ.; edema disappeared in 10 days; urine 20 oz. daily; albumin (tr.) remains
2	2 yrs. 8 mos.	M	37 (2nd ac. attack in 3 mos.)	99.6-103	15.0	Severe gen.; anasarca	8 hematuria	5, 3 hourly	8	640.0	Doubtful	Tonsils enlarged and inflamed; temp. remained 98 to 99° daily for 1 mo. before coming to nor.; edema diminished slowly but some remained on feet; alb., casts and r.b.c.; persisted urine; general condition better
3	1 yr. 2 mos.	M	4	103-104	19.2	Moderate	Anuria (12 hrs.)	Started with 10, after 8th dose reduced to 7, 3 hourly	3	199.0	Recovered	Temp. nor. in 3 days; urine commenced flowing in 6 hrs.; in 12 days urine free from alb. and r.b.c., 20 oz. daily; edema gone in 4 days
4	2 yrs. 6 mos.	M	7	99-101	9.0	Severe	Anuria (10 hrs.)	10, 4 hourly	6	300.0	Recovered	Temp. 97 to 99° for 15 days, then nor.; urine freely passed after 10 hrs., in 8 days free from all abnormalities; edema disappeared in 15 days; general condition fair; anemia receiving treatment
5	7 yrs. 6 mos.	F	4	100-101.8	14.5	Severe	6-7	10, 3 hourly	4	32.0	Recovered	Temp. nor. in 3 days; urine increased to 24 oz. daily in 3 days; no alb., casts or r.b.c.; general condition very good
6	4 yrs. 3 mos.	M	12	99-104	7.6	Severe all over body	Oliguria; hematuria +	10, 3 hourly	2	160.0	Died	Very toxic; bronchopneum. rt. lung; was on sulfadiazine; died without any response to treatment
7	4 yrs. 8 mos.	F	7	100-101	12.5	Moderate	Oliguria, few drops each time	10, 3 hourly	3	24.0	Recovered	Temp. nor. in 2 days; urine flow good in 3 days; in 7 days free from all abnormalities
8	11 mos.	M	8 (3rd attack in 1 mo.)	100-103	14.7	Very severe all over body	4	Started with 10, after 8th dose reduced to 5, 3 hourly	4	200.0	Recovered	Acute pharyngitis present; temp. nor. in 4 days; urine output 25 oz. in 3 days; edema gradually disappeared in 22 days; urine normal
9	1 yr.	M	5	97-100	12.0	Ascites only over feet	8-10	7, 3 hourly	3	168.0	Recovered	Temp. nor. in 3 days; urine output impr. from 1st day, free from alb. and r.b.c. in 7 days; general condition excellent
10	1 mo. 3 yrs.	M	15	98-99.6	10.7	Severe	12	10, 4 hourly	7	420.0	Recovered	Pharyngitis and bronchitis present; temp. nor. in 6 days; urine contained alb. and some r.b.c. for 1 mo.; anemia severe, being treated
11	8 yrs.	F	7	99-102.6	9.5	Moderate	15	10, 3 hourly	5	400.0	Satisfactory	Chronic tonsillitis and adenoids present; temp. 99.4° daily; edema less; urine free, contains alb. (tr.) and some r.b.c.; awaiting tonsillectomy
12	1 yr. 7 mos.	F	14	100-102	15.5	Moderate	10-12	10, 4 hourly	5	300.0	Recovered	Bronchitis present; temp. nor. in 4 days; edema disappeared in 7 days; urine 30 oz. daily, free from alb. and r.b.c. after 15 days; anemia severe, receiving treatment

kidney substance. This results in a virtual decompression of the nephrons, thus enabling more of these units numerically to function normally.

Choice of Cases. In this series, as stated before, 12 children with severe acute nephritis were treated. Almost all were in a critical condition and in some life was despaired of. In some cases evidence of a primary infective focus was demonstrable and in most the leukocyte count was raised. Rise in temperature was present in all. In some complete anuria or oliguria had set in with variable amount of edema. One child had severe hematuria, possibly aggravated by the administration of large doses of sulfadiazine.

Material and Method of Administration. Penicillin was supplied in rubber capped bottles containing 100,000 units in each in the form of a powder. This was dissolved in 10 cc. sterile normal saline and the solution was kept constantly in the refrigerator.

All injections in this series were given intramuscularly. All syringes and needles were sterilized in double distilled water and cooled before use.

The skin at the site of injection and the rubber cap of the bottle were cleaned with ether. The utmost care was taken to avoid leakage of the solution into edematous tissues around the site of injection.

Dosage. The dose per injection varied between 5000 and 10,000 units, administered at 3 hourly, or in some cases 4 hourly, intervals. The total dosage varied between 192,000 and 640,000 units, except in Case 6 which died while treatment was in progress.

Duration of Treatment. The number of consecutive days of treatment varied from 3 to 8. There is no doubt that the duration of treatment required depends to some extent on the length of the period before penicillin therapy is started. It is also evident that the improvement caused was continued long after the actual period of treatment.

Complications. No toxic phenomena or complications arose in any of the cases treated. In 1 case only (Case 11) the child complained of severe headache on the first day of treatment after the fifth injection. This was attributed to systemic

or psychologic causes and was relieved by antispasmodics. Some of the older children became "needle shy" and some difficulty was experienced in continuing the treatment.

Results. In judging the results it is to be remembered that these cases were chosen for the very reason that they were *in extremis* and had failed to respond to any other form of treatment. There remains no doubt that penicillin has a definite place in the treatment of acute nephritis. In the cases which were not complicated by complete anuria but were nevertheless very serious due to the presence of oliguria, the response was remarkable. The temperature came down to normal in 36 to 72 hours and although in some it rose slightly above normal for a few days, the general improvement justified the stoppage of penicillin. The urine improved greatly in output and became free from albumin, casts and red blood cells. In Cases 1, 2 and 11 some abnormality remained in the urine after the end of treatment, but they became afebrile and the edema gradually decreased due to improved urine output. Case 6 was very toxic when treatment was commenced. This was the fourth acute exacerbation within 3 months and during the 12 days previous to this treatment large doses of sulfadiazine had been administered. For 2 days he had hematuria with only a few drops passed at a time. He died after 2 days treatment.

It may be noted that the word "recovered" is used in the table of cases to imply complete absence of symptoms and signs; *e. g.*, rise of temperature, edema, presence of casts, albumin and blood cells in the urine. It does not necessarily mean a permanent eradication of disease.

Summary. Twelve cases of acute nephritis in children have been treated with penicillin, all being of very severe type. There was 1 death after 2 days treatment; the results were satisfactory in the other 11.

The bactericidal action of penicillin is

employed to eliminate the causal infective oration of signs and symptoms are encouraging, and a wider trial is recommended.

Results, as judged by the rapid ameli-

REFERENCES

- ABRAHAM, E. P., GARDNER, A. D., CHAIN, E., FLETCHER, C. M., HEATLY, N. G., and FLOREY, H. W.: *Lancet*, 2, 177, 1941.
- DAWSON, H., and HOBBY, G. V.: *J. Am. Med. Assn.*, 124, 622, 1944.
- FLEMING, A., in discussion on Penicillin, *Proc. Roy. Soc. Med.*, Vol. 37, p. 101,
- FLOREY, M. E., and FLOREY, H. W.: *Lancet*, p. 387, 1943.
- GARROD, L. P.: *Brit. Med. J.*, p. 107, 1945.
- HERRELL, W. E., HEILMAN, D. H., and WILLIAMS, H. L.: *Proc. Staff Meet. Mayo Clin.*, 17, 609, 1942.
- McKEOWN, K. C.: *Brit. J. Surg.*, 31, 13, 1943.
- MORGAN, H. V., CHRISTIE, R. V., and ROXBURGH, I. A.: *Brit. Med. J.*, p. 515, 1944.
- RAMMELKAMP, C. H., and KEEFER, C. S.: *J. Clin. Invest.*, 22, 425, 1943.

PENICILLIN THERAPY IN ULCERATIVE COLITIS*

A PRELIMINARY REPORT

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THIS report is on the results of penicillin therapy in 5 cases of chronic ulcerative colitis. It is realized that this is a small series of cases upon which to base a report; also the subsequent follow-up is admittedly inadequate. However, the immediate beneficial results warrant this report in the hope that others may be encouraged to try a prolonged large scale evaluation of penicillin therapy in this disease.

The present literature considers penicillin ineffective in chronic ulcerative colitis.^{1,7} It is worthwhile considering the literature in regard to the penicillin dosage used in this disease as well as in certain other diseases. Infections due to non-hemolytic streptococci treated with penicillin are almost entirely in cases of subacute bacterial endocarditis. Early attempts to treat this disease with penicillin were unsatisfactory because only small and inadequate doses could be given.⁹ More recent experience, using of 200,000 to 300,000 units a day for 2 to 3 weeks, has indicated at least temporary arrest of the infection in more than 50% of the cases.^{5,10,12} Other infections such as primary syphilis appear amenable to penicillin therapy only in relatively high dosage. In reviewing the literature⁷ it was found that the maximum dose used in ulcerative colitis was 840,000 units of penicillin in a period of 6 days, the average being about 140,000 units per day. It seemed reasonable to try a higher dosage in some cases of ulcerative colitis; a total dosage of 1,200,000 units in 5 days was arbitrarily chosen. The intramuscular route of ad-

ministration was adopted, as it is fully as effective as the intravenous.⁸ It is regretted that laboratory facilities to determine penicillin blood levels were not available. However, in order to establish a sufficiently prolonged and adequate blood level, the dosage was given every 3 hours.^{1,8} Thus, 30,000 units were given intramuscularly every 3 hours up to a total of 1,200,000 units.

We do not infer that the penicillin therapy in these cases was a specific treatment for a disease due to a specific organism. It was simply an attempt to evaluate its effect in cases of chronic ulcerative colitis. The examinations of these patients did not reveal any indication of specific diseases such as bacillary dysentery, amebic colitis, tuberculous colitis, lymphopathia venereum, histoplasma capsulatum infection, or a deficiency syndrome such as sprue. The findings in each case indicated the so-called non-specific or idiopathic colitis. The proctoscopic findings were characteristic of the "streptococcic ulcerative colitis" described by Barger² or the stage 2 or stage 3 of the acute stage of ulcerative colitis as classified by Bockus.³ The lesions began in the most distal segment of the rectum, diffusely involved the entire bowel wall, and showed the characteristic hyperemic, edematous, friable, granular mucosa with scattered areas of ulcerations. It is believed that the colon roentgen-ray findings were not necessary for the diagnosis but did serve in the estimation of the extent and severity of the disease.

* This paper was presented, in abbreviated form, on May 3, 1945, at the AAF Medical District Conference, South Central Medical District, San Antonio Aviation Cadet Center, San Antonio, Texas.

Case Abstracts. **CASE 1.** A white male, 34 years, stated that about 1935 he noticed the onset of severe pains in the umbilical area with radiation to the splenic region associated with alternating attacks of diarrhea and constipation. The color of his stools varied from a light brown to red to black. He was treated at that time by a private physician for colitis. These symptoms occurred intermittently throughout the years. In June, 1943, he developed severe peri-umbilical pains accompanied by approximately 20 bowel movements daily. Gross blood was present in the stools at intervals. Hospitalization was required for a period of 1 week. The diarrhea continued consisting of 5 soft light brown stools a day. The patient was rehospitalized elsewhere on four different occasions. Each time he had complained of 15 to 20 stools daily frequently containing blood. On admission he was having 5 to 10 liquid and soft stools daily usually associated with fresh blood. The intermittent peri-umbilical pain had continued.

The physical examination was essentially negative except for slight tenderness below the umbilicus on abdominal pressure. The red cell count was 4,000,000 with 10 gm. of hemoglobin. The white cell count was 15,200 (77% neutrophils). Repeated stool examinations for parasites and pathogenic organisms were negative. The proctosigmoidoscope was passed 8 inches revealing multiple areas of ulceration throughout. The ulcers were more profuse in the rectum and averaged about 6 mm. in diameter. The mucosa was very hyperemic with occasional areas of pin-point hemorrhage. Mucosal edema and friability were marked. The barium enema revealed redundancy of the sigmoid and descending colon with some lack of haustration; after emptying there was a small amount of barium throughout the colon and a rather stringy appearance suggesting spasticity. There was slight irregularity in the haustration of the distal half of the transverse colon.

The patient was given a high protein, high carbohydrate, low residue diet, multi-vitamins, and ferrous sulfate. Proctosigmoidoscopy was done on the 3d, 10th, and 17th hospital days. The only change noted was a slight decrease in the friability of the mucosa. The 5 day course of penicillin was then given. On the 25th hospital day, 3 days after penicillin was stopped, proctosigmoidoscopy

revealed only slight hyperemia and granularity of the mucosa. The ulcerations and friability previously observed had completely disappeared. On the 43d hospital day, examination revealed no recurrence of the rectal ulcers. One month later, the patient wrote that he was having well-formed stools and he felt greatly improved.

CASE 2. A white, male, 32 years, had noticed since 1935 recurrent episodes of mid-abdominal colic accompanied by watery stools which at times were associated with fresh and old blood. In January, 1944 he had been hospitalized for about 10 days for these symptoms. On admission he was having 5 to 6 stools daily. He described them as watery, yellow, and occasionally red or black. He also complained of a constant tenesmus. He had lost 5 pounds of weight in the past year.

The physical examination was essentially negative except for slight tenderness on pressure over the left lower abdominal quadrant. The urinalysis, complete blood count, and sedimentation rate were within normal limits. Repeated stool examinations for parasites and pathogenic organisms were negative. Proctosigmoidoscopy for a distance of 10 inches revealed numerous ulcerations averaging about 8 mm. in diameter. They were most marked in the caudal half of the rectum. There were at least 15 ulcerative areas, their base being grey or hemorrhagic in type. The mucosa was hyperemic and edematous. The barium enema was essentially negative.

The patient was given a high protein, high carbohydrate, low residue diet, multi-vitamins, and ferrous sulfate. He was placed at bed rest and given an 8 day course of sulfadiazine with an initial dose of 4 gm. and then 1 gm. every 4 hours. A blood "sulfa" level of 10 to 12 mg. was obtained. On the 19th hospital day, 2 days after sulfadiazine was discontinued, proctosigmoidoscopy was repeated. The numerous ulcerations and hyperemia were still present. The following day he was started on the 5 day course of penicillin. Two days after its completion, proctosigmoidoscopy revealed the disappearance of the ulcerations except for 3 small areas which were covered by a superficial thrombus and were apparently healing. The mucosal hyperemia and edema had also disappeared. Examination 5 days later showed no evidence of ulceration. Proctosigmoid-

oscopy 1 month and 2 months later revealed no recurrence of the ulcerations. The patient stated that he felt greatly improved. He was having only 1 or 2 well-formed stools daily with no evidence of bleeding.

CASE 3. A white male, 36 years, while in North Africa in May 1943, developed diarrhea consisting of 15 to 20 watery stools daily some of which contained blood. This persisted for 3 weeks and soon afterward recurred for a period of 1 week. He was treated with oral bismuth preparations and improvement resulted. After feeling well for 2 months, the symptoms recurred. He had 10 to 15 watery bloody stools daily associated with lower abdominal cramping pains. From August 1943 to the latter part of 1944 while in Italy he continued to have frequent loose stools which were sometimes bloody and were associated with abdominal cramps and generalized weakness. Treatment was symptomatic in type. On January 29, 1945, shortly after his return to this country he was hospitalized on our service. He complained of diarrhea averaging 8 liquid or soft stools daily often associated with fresh blood. Lower abdominal cramps were also present.

The general physical examination was essentially negative. The urinalysis and complete blood counts were within normal limits. Repeated stool examinations for parasites and pathogenic organisms were negative. The barium enema Roentgen ray was negative. Proctosigmoidoscopy revealed large external hemorrhoids encircling the anal orifice. The instrument was passed with great difficulty for a distance of only 7½ inches because of the patient's discomfort. The mucosa was extremely redundant, edematous and hyperemic. There were multiple ulcerations averaging about 6 mm. in diameter throughout the area of visualization. The ulcers contain a sero-sanguineous exudate.

He was treated with a high protein, high carbohydrate, low residue diet with multivitamin tablets, bismuth subcarbonate and ferrous sulfate for 2 weeks. By that time he was having about 4 soft stools daily associated with considerable flatus. However, proctosigmoidoscopy revealed essentially no change in the pathologic signs previously described. He was given an 8 day course of sulfadiazine with a blood level of about 10 to 12 mg. per 100 cc. Three days after its completion proctosigmoidoscopy showed no

apparent change in the ulcerations but the mucosa was somewhat less hyperemic and edematous. There was essentially no change in his symptoms. A 10 day course of chiniofon 0.25 gm. t.i.d. was given. At its completion, proctosigmoidoscopy showed no change in the ulcerations and his symptoms remained the same. On his 38th hospital day he was started on the 5 day course of penicillin. On the 45th hospital day, examination revealed apparent healing of all the ulcerations and an essentially normal mucosa except for granularity and redundancy. Proctosigmoidoscopy on the 52nd hospital day revealed the same findings. The stools were formed, there was no excessive flatus, and the rectal bleeding had ceased. Sixty days after the course of penicillin, examination revealed no recurrence of the rectal ulcerations.

CASE 4. A white male, 30 years, in March 1944 suddenly developed a diarrhea consisting of 5 liquid and soft stools daily with some blood streaking, pus and mucus. Two weeks after onset of his symptoms he was hospitalized elsewhere. He stated that a diagnosis of ulcerative colitis was made. During 6 months hospitalization, general therapy and sulfaguanidine resulted in improvement so that he was passing 2 formed stools daily with no gross blood, pus or mucus. After discharge from the hospital in October 1944 he felt well until December 1944 when the same symptoms recurred. He was rehospitalized elsewhere on February 10, 1945. The proctosigmoidoscopy was reported: "Shows multiple small punctate ulcers, bleeding areas surrounding submucosal hemorrhages, and petechiae in moderate numbers." A diagnosis had been made of "severe chronic ulcerative colitis with submucosal hemorrhages." Treatment consisted of a bland low residue diet, vitamin supplements, and sulfaguanidine 2 gm. 4 times daily from February 16 to March 1. He was transferred to this hospital on March 2, 1945.

The physical examination revealed mild, deep, diffuse abdominal tenderness. The edge of the liver was palpable at the costal margin and was slightly tender. He continued to have 3 or 4 liquid or semisolid stools daily with some fresh blood, pus and mucus. There was excessive flatus. Proctosigmoidoscopy (9 inches) revealed multiple ulcerations ranging up to 5 mm. in diameter and containing a seropurulent-hemorrhagic

exudate. There was diffuse hyperemia, numerous pin-point hemorrhages with some areas of larger bleeding, marked edema and increased friability. Using a platinum wire loop under direct visualization cultures were made directly from the ulcers. These were subsequently reported as *E. coli*. Repeated warm stool examinations were negative for parasites and the cultures were negative for pathogenic organisms. The Frei test was negative. The red cell count was 3,770,000 with 11 gm. of hemoglobin. The white cell count, the differential count, and the sedimentation rate were normal. The barium enema revealed an absence of haustral markings in the distal colon. There was no definite serration of the bowel wall and the mucosal pattern of the descending colon was not destroyed. On the 8th hospital day the 5 day course of penicillin was started. No other treatment was given except for the high protein, high carbohydrate, low residue diet. On the 15th hospital day, proctosigmoidoscopy showed apparent healing of all the previous ulcerations. However, multiple pin-point hemorrhagic areas were still present. The mucosa was not as friable and the edema had decreased. The same course of penicillin was repeated in addition to the administration of vitamin supplements, ferrous sulfate, and belladonna rectal suppositories. On the 22d hospital day, proctosigmoidoscopy (10 inches) revealed mild to moderate hyperemia and edema while the hemorrhagic areas were less marked and appeared to be subsiding. No ulcers were present. Mild sedatives, antispasmodics, bismuth subcarbonate, and intramuscular liver were given in addition to the other general therapy. Proctosigmoidoscopy was done at weekly intervals revealing gradual improvement so that on the 52nd hospital day there were only a few pin-point hemorrhages, mild to moderate hyperemia and friability and an increasing diffuse granular appearance of the mucosa. He was having usually 2 fairly well-formed stools daily with only an occasional small amount of blood or mucus. There was no tenesmus or abdominal pain. From the 60th to the 65th hospital days, chiniofon 0.25 gm. q.i.d. was given. It was discontinued then because of increasing diarrhea. Proctosigmoidoscopy on the 78th hospital day revealed definite improvement consisting of decreased hyperemia, edema, and friability, the absence of hemorrhagic

areas, and a slightly granular appearance of the mucosa. There were no ulcerations. The final examination on the 85th hospital day revealed no recurrence of the ulcerations or hemorrhagic areas.

CASE 5. A Negro, 29 years, stated that he had noticed rectal bleeding for 2 years. He had frequent episodes of diarrhea consisting of 6 or 7 soft stools daily. The fresh blood usually discolored the stools and also followed the bowel movement. Tenesmus and abdominal cramps occurred frequently. He had lost 12 pounds of weight in 2 years. An accurate history was difficult to obtain from the patient.

The general physical examination was essentially negative. The red cell count was 3,950,000 with 11.5 gm. of hemoglobin. The white cell count was 7100 with a normal differential count. The serum protein was 7.6 gm. Repeated stool examinations were negative for parasites and pathogenic organisms but revealed large amounts of blood, pus and mucus. A Frei test was negative.

Proctosigmoidoscopy (10 inches) showed diffuse ulcerated, hemorrhagic areas throughout with a well marked polypoid, hyperplastic inflammation most prominent on an adjacent to the lower and middle rectal valves. Biopsies of two of the polypoid lesions revealed microscopically a heavy diffuse and focal round cell infiltration with numerous eosinophiles throughout the mucosa and subjacent fibrous and muscular tissues. The appearance indicated no specific type of histopathologic lesion and the diagnosis was chronic proctitis. The patient was afebrile but it was considered inadvisable to attempt a barium enema Roentgen ray because of the above findings and his general condition.

Treatment consisted of a high protein, high carbohydrate, low residue diet, phenobarbital, belladonna, ferrous sulfate and multivitamin tablets. An initial dose of 4 gm. of sulfadiazine and 1 gm. every 4 hours were given for 6 days. Three days later, on the 23d hospital day, proctosigmoidoscopy revealed essentially no change. Chiniofon 0.25 gm. t.i.d. was prescribed for 10 days. Again the examination was unchanged. The 5 day course of penicillin was given. On the day it was completed, proctosigmoidoscopy showed only a few remaining ulcerations on the valves of Houston and a marked decrease in the hyperplastic inflammation, friability,

edema and hyperemia. Examination 7 days later revealed no definite ulcerations although a few superficial erosions were present on the rectal valves. The proliferative granulations had decreased. A 2d course of penicillin was given in the increased dosage of 40,000 units every 3 hours for 10 days. Proctosigmoidoscopy then revealed a decrease in the degree and extent of the polypoid granulating areas and some local hyperemia and friability still persisted. No ulcerations were present. Symptomatically the patient was much improved. He had no cramps or tenesmus. He still had 2 to 4 soft stools daily with occasionally a little fresh blood. He had gained 14 pounds of weight since the institution of penicillin therapy.

Discussion. Chronic ulcerative colitis is a disease of unknown cause. The term probably embraces a group of variable colon and systemic signs and symptoms depending on how different individuals react to a single injurious agent or it involves a similar syndrome resulting from multiple etiologic agents. The course of the disease is extremely varied and unpredictable. Improvement both subjectively and objectively in response to a new form of therapy may be purely coincidental to the natural history of the disease in individual cases. It may be influenced by psychogenic factors incident to the hope of a new effective treatment. The enthusiasm of the physician as well as the patient may be of considerable effect in a partial or total psychosomatic disorder. Only on such a basis can any new type of therapy be properly evaluated.

At the present time there is no widely accepted specific treatment for this disease. Diet, sulfonamides, serums, vaccines, vitamins, and many other agents have been employed. There is no doubt that each has contributed to the improvement or possibly "cure" in many cases. Yet not one of these agents has been considered to have a specific curative effect in a significant number of instances. Many of these measures were used at various stages in conjunction with penicillin therapy in our patients. There seems little doubt that whatever benefit penicillin may exert it

will be increased by other measures, especially those designed to correct the primary or secondary nutritional defects.

These patients were all considered to be moderate to severe cases as regards the extent and degree of the local disease. However, none were severe from the standpoint of systemic reaction. They did not represent either the acute severe fulminating septic type, nor the severe chronic continuous type with a narrowed, shortened fibrotic colon. It will be noted that one case was given preliminary dietary and nutritional therapy for 2 weeks without improvement. The 2d case was given iron and sulfadiazine in addition to nutritional therapy without appreciable benefit. The 3d and 5th cases were given preliminary sulfadiazine and chiniofon therapy without any change in the rectal ulcerations. The 4th case was treated without preliminary therapy (although he had sulfaguandine, vitamins, and a low residue diet at another hospital) and his supportive therapy was given following the initial course of penicillin.

In the 5 cases there was disappearance of all ulcerations during or immediately following the administration of penicillin. This result was the striking feature of the penicillin therapy. The 4th case still had residual pin-point hemorrhages, slight edema, hyperemia, friability, and granularity (all these latter signs being greatly improved over the initial examination). The 5th case still had mild friability and hyperplastic granulations. Additional penicillin therapy did not seem to effect as rapid or possibly as complete disappearance of these pathologic signs. These cases were considerably improved symptomatically while the first 3 patients obtained complete relief. In our experience with these types of cases, the rapid improvement in the proctosigmoidoscopic findings has rarely if ever occurred under any former therapeutic regimen. The duration of follow-up is inadequate for any long term evaluation at this time. However, even the immediate beneficial effect is of considerable importance. It is hoped that a more complete

conclusive report may be published later. At the present time penicillin apparently produces at least a remission in some mild and moderately severe cases of chronic ulcerative colitis and effects an improvement in other moderately severe cases. Arrest of the inflammatory process is the maximal benefit conceivable in those having irreversible fibrotic changes in the bowel wall.

The explanation for the effectiveness of penicillin is not clear. Possibly it acts within the tissues of the bowel wall on one or more of the infective agents such as penicillin susceptible streptococci. It is the usual belief that within the lumen of the bowel penicillin is rapidly inactivated by the intestinal bacteria.¹ However, there is a recent report of penicillin administered in rectal suppositories resulting in sustained blood levels.¹¹ It does not follow necessarily that it would be effective as a local application in inflammatory rectosigmoid lesions, but through its systemic action may be effective by the rectal route. The optimum dosage is still unknown. As in subacute bacterial endocarditis higher dosage over a longer period than 5 days

may increase its effectiveness in ulcerative colitis. We contemplate trying the administration of 40,000 units every 2 or 3 hours for 10 days in a few cases. Recent reports indicate that the more convenient oral route of administration may be practical under some conditions.^{4,6}

Summary. Penicillin in dosages of 30,000 units intramuscularly every 3 hours for 5 days up to a total of 1,200,000 units was administered to 5 cases of chronic ulcerative colitis.

The disappearance of the rectal ulcerations in each case within 1 week after the completion of one course of penicillin was the prominent feature. Improvement also occurred in the other pathologic signs. Improvement in subjective symptoms and the character of the stool was marked in each instance.

The results in these few cases indicate that adequate penicillin therapy may be of considerable value in the treatment or control of some cases of chronic ulcerative colitis. A trial of high dosage penicillin therapy on a large scale with a prolonged case follow-up is believed justified.

REFERENCES

1. ANDERSON, D. G.: The Treatment of Infections With Penicillin, *New England J. Med.*, **232**, 400, 423, 1945.
2. BARGEN, J. A.: The Medical Management of Ulcerative Colitis, *J. Am. Med. Assn.*, **126**, 1009, 1944.
3. BOCKUS, H. L.: *Gastroenterology*, Philadelphia, Saunders, **2**, 573, 1944.
4. BURKE, F. G., ROSS, S., and STRAUSS, C.: Oral Administration of Penicillin, *J. Am. Med. Assn.*, **128**, 83, 1945.
5. DAWSON, M. H., and HUNTER, T. H.: Treatment of Subacute Bacterial Endocarditis With Penicillin, *J. Am. Med. Assn.*, **127**, 129, 1945.
6. GYORGY, P., VANDEGRIFT, H. N., ELIAS, W., COLIO, L. G., BARRY, F. M., and PILCHER, J. D.: Administration of Penicillin by Mouth, *J. Am. Med. Assn.*, **127**, 639, 1945.
7. HARTFORD, C. G., MARTIN, S. P., HAGEMAN, P. O., and WOOD, W. B., JR.: Treatment of Staphylococci, Pneumococci, Gonococci, and Other Infections With Penicillin, *J. Am. Med. Assn.*, **127**, 253, 1945.
8. HERRELL, W. E., NICHOLS, D. R., and HEILMAN, D. H.: Penicillin: Its Usefulness, Limitations, Diffusion, and Detection, With Analysis of 150 Cases in Which It Was Employed, *J. Am. Med. Assn.*, **125**, 1003, 1944.
9. KEEFER, C. S., *et al.*: Cited by Anderson.¹
10. LOEWE, L., ROSENBLATT, P., GREENE, H. J., and RUSSEL, M.: Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis: Report of Seven Consecutive Successfully Treated Patients, *J. Am. Med. Assn.*, **124**, 144, 1944.
11. LOEWE, L., ALTURE-WERBER, E., and ROSENBLATT, P.: Administration of Penicillin by Rectal Suppository, *J. Am. Med. Assn.*, **128**, 18, 1945.
12. MEADS, M., HARRIS, H. W., and FINLAND, M.: Cited by Anderson.¹

COMBINED PENICILLIN AND SULFADIAZINE THERAPY IN PNEUMOCOCCIC PNEUMONIA*

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NUMEROUS reports have already established the value of penicillin in the treatment of pneumococcic infections.^{6,8,9,11} It is the purpose of this study to evaluate further the effectiveness of penicillin in the treatment of pneumococcic pneumonia by comparing 2 series of cases similar in severity of the disease cared for in the same hospital by the same staff and treated with the same general therapeutic routine. The only variation in treatment was that severely ill patients in the first group received adjuvant type specific anti-pneumococcic serum, while for similar indications a comparable number in the second group received adjuvant penicillin.

In the period from September 1, 1943 to May 1, 1945, 1620 consecutive patients with pneumococcic pneumonia were treated at the Permanente Foundation Hospital. The diagnosis of pneumonia was substantiated in every case by indisputable physical findings and a positive chest roentgenogram. No case in which the diagnosis of pneumonia could be questioned was included in this series. Patients with pneumonia as a contributory diagnosis to another illness were excluded. Sputum examinations in every case showed the predominant organism to be the pneumococcus. Specific typing by Neufeld method was obtainable in 70% of cases.

Procedure. The general therapeutic regimen which was followed in this hospital for the treatment of pneumococcic pneumonia has been outlined elsewhere.³ Every patient who was moderately or severely ill received maximum therapeutic doses of sulfadiazine,

since it has been demonstrated⁴ that the use of higher doses of sulfadiazine resulted in a marked decrease in mortality rate, a decrease in incidence of common complicating conditions, and a decrease in length of hospital stay, without any notable changes in incidence of drug toxicity. Hence, the majority of patients received an initial dose of 5 gm. of sodium sulfadiazine in 500 cc. of $\frac{1}{6}$ molar solution of sodium lactate intravenously followed by sufficient sulfadiazine administered orally to maintain average blood sulfadiazine concentrations from 12 to 20 mg. per 100 cc.⁴ Adjuvant therapy in the form of fluids, expectorant cough mixtures, oxygen inhalation, and alkali (sodium bicarbonate, sodium lactate, or potassium bicarbonate as indicated) were used routinely.

Comparative Therapeutic Efficacy of Combined Penicillin and Sulfadiazine Therapy. From May 1, 1944 to May 1, 1945, 872 patients with pneumococcic pneumonia were treated as outlined above. Of these patients 195 (22.4%) were treated with penicillin in addition to sulfadiazine for indications presented below. In this group of 872 patients, 13 (1.5%) died (Table 1). All deaths occurred among the 195 severely ill patients who had received combined therapy.

In the previous 8 month period from September 1, 1943 to May 1, 1944, 748 patients with pneumococcic pneumonia were treated with the same general therapeutic regimen. The only differences in treatment were that (1) no penicillin was used, and (2) type specific pneumococcic serum was used in 156 (20.9%) of cases. In this group of 748 patients, 46 (6.2%)

* Statistics compiled by Martha Eaton, A.B.

died (Table 1). Forty-two of these deaths occurred among the 156 patients who were severely ill and were treated with combined serum and sulfadiazine therapy.

It is important to note from Table 1 that the patients in both series who received only sulfadiazine were of approximately the same frequency and same negligible mortality.

These results indicate that in the treatment of pneumococcic pneumonia with sulfadiazine, the adjuvant use of penicillin in place of specific serum in severely ill patients resulted in a decrease in mortality rate from 26.9% to 6.7%. The over-all mortality rate for pneumococcic pneumonia was decreased from 6.2 to 1.5%.

illin therapy. It is important to note that penicillin is extremely effective in the treatment of pneumococcic Type III pneumonia.

Comparative Age of Patients. As is demonstrated in Table 3, the age of a patient is a very important factor influencing mortality in pneumonia. Table 3 further shows that the comparative incidence according to age agrees very closely in the two series. It is of interest that 51% of the patients in both series were over forty years of age. In the penicillin treated series the per cent mortality was lower in every decade.

Comparative Severity of Associated Diseases. Obviously the presence of an asso-

TABLE 1.—COMPARATIVE MORTALITY RATES, 1620 CASES OF PNEUMOCOCCIC PNEUMONIA, WITH SULFADIAZINE AND PENICILLIN OR SERUM AS ADJUVANT THERAPY

Therapy	No. cases	% incidence	No. deaths	% mortality
Sulfadiazine only	677	77.6	0	0.0
Penicillin and sulfadiazine	195	22.4	13	6.7
Total	872	100.0	13	1.5
Sulfadiazine only	592	79.1	4	0.7
Serum and sulfadiazine	156	20.9	42	26.9
Total	748	100.0	46	6.2

Comparative Severity of the Two Series. Since gross mortality statistics have little comparative value unless the series of cases represents illnesses of approximately equal severity, these two groups were analyzed as to the severity of the various important factors which influence the mortality in pneumococcic pneumonia.

It has already been shown (Table 1) that the two series were of similar clinical severity, since about 78% of each group was judged of insufficient severity to require adjuvant therapy, and the fatality rate was comparably negligible in these groups treated with sulfadiazine only.

Comparative Incidence and Mortality Rates of Specific Pneumococcic Types. It is apparent from Table 2 that the same specific pneumococcic types predominated in both groups; furthermore, in each type a marked decrease in the per cent mortality occurred with the addition of penic-

ciated disease may be very important in influencing the mortality of pneumonia. The grading of the severity of an associated disease is difficult and depends upon the judgment of the examiner. Some uniformity of grading was attempted by grading an associated disease as "mild" if it was sufficiently severe to aggravate or alter the course of the pneumonia, "moderate" if it was sufficiently severe so that associated with pneumonia it might jeopardize the life of the patient, and "severe" if the associated disease was in itself sufficient to endanger the life of the patient. Table 4 shows that associated diseases were present with about the same frequency in both groups. Although associated diseases graded as "severe" were less frequent in the penicillin treated series, it is apparent that the marked decrease in mortality in this group is

primarily due to adjuvant penicillin therapy.

Tables 1 through 4 indicate that these two series of cases represent groups of approximately equal severity, and therefore their mortality statistics can be directly compared.

Comparative Incidence of Complicating Conditions. As shown in Table 5 the incidence of important complicating conditions was equally low in the two series. Except for an increased frequency of sterile

effusions, the additional use of penicillin did not materially alter the incidence of common complicating conditions.

Pleural empyema developed in 1 patient in the penicillin treated group. Injections of penicillin into the empyema cavity failed to cure the infection and a rib resection with drainage was performed resulting in prompt recovery.

Serofibrinous pericardial effusions developed in 3 patients as evidenced by the recognition of a pericardial friction rub,

TABLE 2.—COMPARATIVE INCIDENCE AND MORTALITY OF COMMON SPECIFIC PNEUMOCOCCIC TYPES

Pneumo. type	No. cases	% incidence	No. deaths	% mortality	Pneumo. type	No. cases	% incidence	No. deaths	% mortality
A. Combined Penicillin and Sulfadiazine Therapy (195 Cases)					B. Combined Serum and Sulfadiazine Therapy (156 Cases)				
VII	33	16.9	1	3.0	VII	50	32.2	9	18.0
III	27	13.8	2	7.4	III	30	19.3	15	50.0
I	22	11.3	1	4.5	I	17	10.9	4	23.5
IV	15	7.7	2	13.3	V	10	6.4	2	20.0
VIII	13	6.7	0	0.0	VIII	10	6.4	0	0.0
XII	10	5.1	1	10.0	XXV	10	6.4	0	0.0
II	9	4.6	1		XII	7	4.5	2	
V	8	4.1	1		II	6	3.8	2	
XXV	5	2.6	1		IV	6	3.8	4	
XXIV	3	1.5	0		XX	4	2.6	0	
VI	2	1.0	0		XXIV	2	1.3	1	
X	2	1.0	0		VI	1	0.6	0	
XIV	2	1.0	1		XIV	1	0.6	0	
XVII	2	1.0	0		XIX	1	0.6	1	
XXXIII	2	1.0	0						
C. Sulfadiazine With Adjuvant Penicillin Therapy (872 Cases)					D. Sulfadiazine With Adjuvant Serum Therapy (748 Cases)				
VII	81	9.3	1	1.3	VII	92	12.3	10	10.9
I	71	8.1	1	1.4	XXV	55	7.4	1	1.8
III	46	5.3	2	4.3	I	52	7.0	6	11.5
XXV	43	4.9	1	2.4	III	47	6.3	16	34.0
IV	41	4.7	2	4.2	V	45	6.0	2	4.4
VIII	41	4.7	0	0.0	VIII	32	4.3	0	0.0
V	35	4.0	1	2.9	IV	31	4.1	4	12.9
XII	35	4.0	1	2.9	XII	30	4.0	2	6.7
II	29	3.3	1	3.4	XXIV	13	1.7	1	7.7
XXIV	27	3.1	0		XXXII	13	1.7	0	
XX	20	2.3	0		XX	11	1.5	0	
IX	13	1.5	0		XXXIII	11	1.5	0	
VI	12	1.4	0		II	10	1.3	2	
XVIII	12	1.4	0		XVIII	10	1.3	0	
XIII	11	1.3	0		XIX	10	1.3	1	

TABLE 3.—COMPARATIVE INCIDENCE AND MORTALITY BY AGE

Age (yrs.)	No. cases	% incidence	No. deaths	% mortality	No. cases	% incidence	No. deaths	% mortality
A. Combined Penicillin and Sulfadiazine Therapy					B. Combined Serum and Sulfadiazine Therapy			
Under 20	7	3.6	0	0.0	6	3.8	0	0.0
20-29	27	13.8	0	0.0	22	14.1	3	13.6
30-39	33	16.9	1	3.0	30	19.2	4	13.3
40-49	53	27.2	4	7.7	34	21.9	10	29.4
50-59	43	22.1	6	14.0	45	28.9	17	35.6
60-69	25	12.8	1	4.0	18	11.5	7	38.9
70 and over	7	3.6	1	14.3	1	0.6	1	100.0
Total	195	100.0	13	6.7	156	100.0	42	26.9
C. Sulfadiazine With Adjuvant Penicillin Therapy					D. Sulfadiazine With Adjuvant Serum Therapy			
Under 20	45	5.2	0	0.0	49	6.6	0	0.0
20-29	157	18.0	0	0.0	141	18.8	3	2.1
30-39	221	25.4	1	0.5	177	23.7	5	2.8
40-49	209	24.0	4	1.9	172	22.9	10	5.8
50-59	145	16.6	6	4.1	126	16.9	18	14.3
60-69	85	9.7	1	1.2	75	10.0	9	12.0
70 and over	10	1.1	1	10.0	8	1.1	1	12.5
Total	872	100.0	13	1.5	748	100.0	46	6.2

roentgenographic demonstration of a transitory diffuse enlargement of the heart, and characteristic changes in the electrocardiogram. In each of these patients the pericardial effusion absorbed spontaneously. No instances of meningitis developed in either series.

Comparative Length of Hospital Stay. Excluding fatal cases, about two-thirds of the patients in each group had recovered from their acute illness and were discharged from the hospital in less than 7 days (Table 6). Only about 8% of patients in each group required over 14 days of hospital care. No remarkable

impending pulmonary edema or shock, with severe toxic delirium, with a leukocyte count below 6000 cells per cmm;⁷ or other evidence of severe infection or toxicity.

2. Failure to respond to adequate dosage of sulfadiazine (studies^{8,9} have demonstrated sulfadiazine-fast pneumococci to be readily susceptible to penicillin).

3. Pneumococcic Type III pneumonia in patients over 40 years of age.

In the above groups, not only were maximum doses of penicillin given in order to obtain immediate antibacterial action,⁴ but high blood concentrations of sulfa-

TABLE 4.—COMPARATIVE SEVERITY OF ASSOCIATED DISEASES

Associated diseases (grade severity)	No. cases	% incidence	No. deaths	% mortality	No. cases	% incidence	No. deaths	% mortality
<i>Sulfadiazine With Adjuvant Penicillin Therapy</i>				<i>Sulfadiazine With Adjuvant Serum Therapy</i>				
Present	193	22.1	9	4.7	142	19.0	15	10.6
Mild	100	51.8	1	1.0	34	36.3	2	5.9
Moderate	77	39.9	5	6.5	43	46.2	0	0.0
Severe	16	8.3	3	18.8	16	17.2	12	75.0
Total (graded)	193	100.0	9	4.7	93	100.0	14	15.1
Severity not graded	0				49		1	2.0
Not present	679	77.9	4	0.6	606	81.0	31	5.1
Total	872	100.0	13	1.5	748	100.0	46	6.2

TABLE 5.—COMPARATIVE INCIDENCE OF COMPLICATING CONDITIONS

Complication	Sulfadiazine with adjuvant penicillin therapy		Sulfadiazine with adjuvant serum therapy	
	No. cases	% incidence	No. cases	% incidence
Sterile effusion	47	5.4	20	2.7
Empyema	1	0.1	2	0.3
Lung abscess	2	0.2	4	0.6
Pericarditis	3	0.3	2	0.3
Endocarditis	0	0.0	2	0.3

difference in length of hospital stay was noted for severely ill patients treated with penicillin as compared with those treated with serum.

Indications for Penicillin Therapy. Although it is likely that in the future, penicillin will be administered routinely to all patients with pneumococcic pneumonia, the restricted supply of penicillin during the past year has limited the use of the drug to severely ill patients only.

In this series of cases, indications for combined penicillin and sulfadiazine therapy were:

1. Patients with high pneumococci counts in their sputum, with evidence of

diazine were also maintained, since it has been shown that combined sulfonamide and penicillin therapy is more effective than either sulfadiazine or penicillin alone.^{7,14}

Penicillin therapy *alone* was given to patients with:

1. A previous history of sulfonamide sensitivity or who developed sensitivity to sulfadiazine before the pneumonic process had cleared.

2. Cardiac failure, renal insufficiency, or acidosis.

Penicillin Administration. In the majority of patients who received penicillin, the drug was administered intramus-

cularly in doses of 25,000 units every 3 hours. To prolong the effect of penicillin by delaying the rate of absorption (and to decrease the pain of repeated injections), ice bags were applied to the site before and after the injection.¹³ The penicillin was administered in a solution of physiologic saline or of 5% glucose in water.¹ Frequently the penicillin was given in doses of 100,000 to 200,000 units daily by continuous intravenous drip. The dosage and mode of administration varied with the severity of the illness; critically ill patients were given

higher doses more frequently. Continuous intravenous drip appeared to be the most efficient method of administration.¹⁰

The majority of patients received a total of about 500,000 units of penicillin. A small group of patients who died shortly after admission received less than 100,000 units because of the short period of treatment (Table 7).

Penicillin therapy was usually continued until the patient was afebrile at least 48 hours. To avoid relapses it was found necessary to continue penicillin administration for a somewhat longer

TABLE 6.—COMPARATIVE LENGTH OF HOSPITAL STAY (EXCLUSIVE OF DEATHS)

Hospital days	No. cases	% incidence	No. cases	% incidence
	<i>A. Combined Penicillin and Sulfadiazine Therapy</i>		<i>B. Combined Serum and Sulfadiazine Therapy</i>	
Under 7	49	26.9	24	21.1
7-14	80	44.0	53	46.5
15-21	20	11.0	20	17.5
22-28	11	6.0	5	4.4
Over 28	22	12.1	12	10.5
Total	182	100.0	114	100.0
	<i>C. Sulfadiazine With Adjuvant Penicillin Therapy</i>		<i>D. Sulfadiazine With Adjuvant Serum Therapy</i>	
Under 7	582	67.8	461	65.8
7-14	204	23.7	184	26.1
15-21	32	3.7	29	4.1
22-28	18	2.1	11	1.6
Over 28	23	2.7	17	2.4
Total	859	100.0	702	100.0

TABLE 7.—PENICILLIN THERAPY

	No. cases	% incidence	No. deaths	% mortality
<i>A. Method of administration:</i>				
Intravenous	30	15.4	3	10.0
Intramuscular	90	46.2	5	5.6
Intravenous and intramuscular	75	38.4	5	6.7
Total	195	100.0	13	6.7
<i>B. Total dosage (units):</i>				
Less than 100,000	10	5.1	2	20.0
100,000-499,000	100	51.3	7	7.0
500,000-1,000,000	55	28.2	1	1.8
More than 1,000,000	30	15.4	3	10.3
Total	195	100.0	13	6.7
<i>C. Toxic reaction:</i>				
Local	7	3.6	0	0.0
General: Urticaria	2	1.0	0	0.0
Dermatitis	1	0.5	0	0.0
Fever	1	0.5	0	0.0
No reaction	184	94.4	13	7.1
Total	195	100.0	13	6.7

period than was ordinarily considered as sufficient for sulfadiazine. This may be because penicillin is excreted within a few hours, whereas therapeutic doses of sulfadiazine are not entirely excreted within 24 hours. Tillett¹² also advised continuing penicillin therapy for at least 3 to 4 days of illness so as to avoid relapses due to discontinuing the drug before the development of type specific immunity.

Toxic reactions to penicillin were rare, but about 10% of patients receiving intravenous penicillin developed local thrombophlebitis. Two patients developed generalized urticaria which promptly cleared after cessation of penicillin therapy. One patient developed a maculopapular and vesicular itching eruption on the 9th day of therapy which spread from the trunk to thighs in spite of discontinuing sulfadiazine and all medications except penicillin; the eruption cleared on the 15th day, 2 days after stopping penicillin therapy. One patient developed a febrile reaction; after this patient had a normal temperature for 3 days, 60,000 units of penicillin as a test dose were administered intramuscularly over a 12-hour period and a transitory rise in temperature to 100.5° F. resulted.

Causes of Failure in Treatment. Of the 13 patients in this series who died, 5 were admitted to the hospital *in extremis* with signs of pulmonary edema and severe shock, and died 4, 8, 9, 15 and 17 hours following admission. The 1st of these patients had associated rheumatic heart disease with early congestive failure and chronic glomerulonephritis (confirmed by autopsy). The 2d was a severe chronic alcoholic. The 3d was also a severe chronic alcoholic, with advanced hepatic cirrhosis (confirmed by autopsy).

The 6th fatal case, a patient aged 43, with a pneumococcic Type XXV pneumonia involving the entire right lung had associated hypertensive heart disease (confirmed at autopsy) with a 6 months history of paroxysmal nocturnal dyspnea. Although he was

treated with high doses of sulfadiazine (attaining a blood concentration of 26.3 mg. per 100 cc.) and 200,000 units of penicillin intravenously daily, he failed to respond and died 36 hours after admission.

The 7th fatal case was that of a patient aged 58 with extensive right upper lobe pneumonia. Sputum examination showed the presence of much mixed infection, but many pneumococci were present which did not react to sera Types I to XXXIII. The patient was a confirmed chronic alcoholic, and was obviously jaundiced on admission, with a large, tender, palpable liver and an ieterus index of 19.7 units. He was treated with sulfadiazine in high doses (attaining a blood concentration of 24 mg. per 100 cc.) and penicillin up to 300,000 units daily. He showed no evidence of response to therapy, rapidly going into pulmonary edema and shock and died 43 hours after admission. Autopsy revealed the presence of a markedly fatty liver.

The 8th patient, aged 62, was admitted with pneumococcic Type IV pneumonia involving the left lower lobe and the entire right lung. He was treated with high doses of sulfadiazine and penicillin, but died 30 hours after admission. Autopsy examination revealed the presence of carcinoma of the stomach, postoperative, with recurrence and metastases to liver, pancreas, and retroperitoneal lymph nodes.

The 9th fatality, a 59 year old man with chronic lymphatic leukemia with leukemic pulmonary infiltrations (confirmed at autopsy) was admitted with pneumococcic Type III lobar pneumonia. He was treated with large doses of sulfadiazine (blood level 22.4 mg. per 100 cc.) and penicillin (200,000 units daily) without response, and died in pulmonary edema 5 days after admission.

Although the 6th, 7th, 8th and 9th fatal cases might have benefited by massive doses of penicillin, the fulminating nature of the pneumonia and the severity of the associated diseases made recovery in each case unlikely. This problem has been presented by Bloomfield *et al.*²

The 10th patient, aged 74, with pneumococcic Type I bacteremia and pneumonia involving the left lower lobe, received sulfadiazine on the 1st day of treatment only because of associated diseases. Although

the patient received 25,000 units of penicillin intramuscularly every 3 hours during his entire hospital stay, he failed to respond to therapy and died on the 6th day.

The 11th fatal case, a patient aged 59, with bilateral pneumococcic pneumonia, was treated with moderate doses of sulfadiazine for 3 days, during which time a sulfadiazine blood level was 6.6 mg. per 100 cc. On the 4th day high doses of sulfadiazine were administered, and on the 5th day he was started on continuous intravenous drip of penicillin, receiving 200,000 units daily. However, the pneumonia spread rapidly and the patient died with pulmonary edema on the 6th day.

The 10th patient, above, did not receive the benefit of combined sulfadiazine and penicillin therapy. The 11th patient was treated with too low levels of sulfadiazine the first few days; at present with the more generous amounts of penicillin available, penicillin also would probably have been started much earlier.

The 12th patient, aged 54, with pneumococcus Type III pneumonia involving the entire right lung, also had a leukopenia of 1600 white cells per cmm. High doses of sulfadiazine were administered (reaching blood concentrations to 33 mg. per 100 cc.) and penicillin intermittently in doses of 25,000 units intramuscularly. After several days of therapy, the patient was unimproved, and the sputum was still loaded with Type III pneumococci. Sulfathiazole was then administered because the organism was obviously sulfadiazine-resistant, but no response was noted. The patient died on the 14th hospital day in pulmonary edema, with a complicating sterile right pleural effusion.

It is evident that the organisms in this patient were sulfonamide-fast, and much larger doses of penicillin by continuous intravenous drip might have been of value.

The 13th fatal case was a patient 40 years of age, with bilateral pneumococcic Type II pneumonia who was treated with high doses of sulfadiazine (blood concentration 16.4 mg. per 100 cc.) for 7 days. Sulfathiazole was begun on the 8th day because of his failure to improve, and discontinued on the 14th day because of the development of a severe sulfathiazole rash. Penicillin had been ad-

ministered by continuous intravenous drip, averaging 150,000 units daily beginning on the 5th hospital day. In addition, because the organisms were obviously sulfonamide and penicillin resistant, on the 15th day 200,000 units of pneumococcic Type II serum were administered. The patient also had an associated acute glomerulonephritis (confirmed at autopsy) with progressive uremia, and developed an acute pericarditis with effusion. The patient died on the 20th day in a state of uremia.

This patient might have benefited by larger doses of penicillin; however, at the autopsy examination it was obvious that the associated glomerulonephritis in itself might have been fatal.

A review of these fatal cases indicated that causes of failure in combined sulfadiazine and penicillin therapy were due to:

1. Patients who were admitted to the hospital *in extremis* and died within a few hours.

2. Inadequate doses of either sulfadiazine or penicillin, or both, due to:

- (a) Inadvisability of administration because of drug sensitivity;

- (b) Insufficient amount of drug given, or

- (c) Development of resistance of the organism to the blood concentrations of drug present.

3. The presence of severe associated diseases which in themselves could be fatal.

Summary and Conclusions. An analysis of 1620 consecutive patients with pneumococcic pneumonia indicated that combined penicillin and sulfadiazine therapy was most effective, with a resultant gross mortality rate of 1.5%.

Penicillin was very effective in the treatment of Type III pneumococcic pneumonia.

The use of penicillin did not decrease the incidence of complicating conditions nor shorten the length of hospital stay.

Details of penicillin therapy were outlined, including its indications, modes of administration, dosage, toxic reactions, and causes for failure of treatment.

REFERENCES

1. ARMSTRONG, C. D., HALPERN, R. M., and CUTTING, W. C.: Prolongation of the Action of Penicillin After Intramuscular Injection, *Proc. Soc. Exp. Biol. and Med.*, **58**, 74, 1945.
2. BLOOMFIELD, A. L., KIRBY, W. M. M., and ARMSTRONG, C. D.: A Study of "Penicillin Failures," *J. Am. Med. Assn.*, **126**, 685, 1944.
3. COLLEN, M. F., and DYBDahl, G. L.: The Management of Pneumonia, *Permanente Foundation Med. Bull.*, **1**, 14, 1943.
4. COLLEN, M. F., and PHILLIPS, E.: Optimum Dosage of Sulfadiazine in the Treatment of Pneumococcal Pneumonia, *Arch. Int. Med.*, **76**, 22, 1915.
5. COLLEN, M. F., DYBDahl, G. L., and O'BRIEN, G. F.: A Study of Pneumonia in the Shipbuilding Industry, *Am. J. Indust. Hyg. and Toxicol.*, **26**, 1, 1944.
6. HARFORD, C. G., MORTIN, S. P., HOGEMAN, P. O., and WOOD, B. W.: Treatment of Staphylococci, Pneumococci, Gonococci, and Other Infections With Penicillin, *J. Am. Med. Assn.*, **127**, 253, 1945.
7. KOLMER, J. A.: *Penicillin Therapy*, New York, Appleton-Century, p. 82, 1945.
8. MCKEE, C. M., and RAKE, G.: Activity of Penicillin Against Strains of Pneumococci Resistant to Sulfonamide Drugs, *Proc. Soc. Exp. Biol. and Med.*, **51**, 275, 1942.
9. POWELL, H. M., and JAMIESON, W. A.: Response of Sulfonamide-fast Pneumococci to Penicillin, *Proc. Soc. Exp. Biol. and Med.*, **49**, 387, 1942.
10. RANTZ, L. A., and KIRBY, W. M. M.: The Absorptions and Excretion of Penicillin Following Continuous Intravenous and Subcutaneous Administration, *J. Clin. Invest.*, **23**, 789, 1944.
11. SAMPER, B. A., and FINLAND, M.: Present Day Specific Treatment of the Pneumonias, *Med. Clin. North America*, **28**, 1067, 1944.
12. TILLET, W. S., CAMBIER, M. J., and MCCORMACK, J. F.: The Treatment of Lobar Pneumonia and Pneumococcal Empyema With Penicillin, *Bull. New York Acad. Med.*, **20**, 142, 1944.
13. TRUMPER, M., and HUTTER, H. M.: Prolonging Effective Penicillin Action, *Science*, **100**, 432, 1944.
14. WARING, J. A., and SMITH, M. H.: Combined Penicillin and Sulfonamide Therapy in the Treatment of Pneumococcal Meningitis, *J. Am. Med. Assn.*, **126**, 418, 1944.

THE INFLUENCE OF SULFANILAMIDE THERAPY UPON THE COURSE OF ACUTE GLOMERULONEPHRITIS IN CHILDREN

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IDEALLY the treatment of acute glomerulonephritis during the initial stage of the disease should control the agent responsible for the initiation of the disease and correct the biochemical and physiologic derangements brought about by the disease. This report deals solely with the results obtained in the attempt to influence the process which is almost universally believed to be related causally to the disease, *viz.*, focal infection. The bacteriologic and immunologic studies of Longcope² and his coworkers have firmly established the opinion which Löhlein¹ stated in 1907, that streptococcal infection precedes with great frequency the onset of acute glomerulonephritis. Because of the finding of infection with the beta hemolytic streptococcus in the majority of cases of acute glomerulonephritis, it is now widely held that extrarenal focal infection with this organism is usually responsible for the production of the disease in the kidneys.

This study, begun in 1938, reports the influence of therapy with sulfanilamide, a drug highly effective against the beta hemolytic streptococcus, upon the course of 33 patients with acute glomerulonephritis. When less toxic sulfonamide compounds became available, they were not substituted for sulfanilamide because of the desire to avoid the complicating crystalluria and hematuria attending the use of these compounds, a complication which is rarely if ever caused by sulfanilamide. In addition, the low renal toxicity of sulfanilamide demonstrated by Marshall and Emerson⁴ would recommend this drug

as a safe chemotherapeutic agent in a patient with renal disease. Forty patients with acute glomerulonephritis to whom sulfanilamide was not administered but who were treated similarly in all other respects served as a control group. The control group of 40 patients formed the basis for a previous report on the criteria for clinical recovery in acute glomerulonephritis in children.⁶ In assessing recovery from acute glomerulonephritis in children we have employed measures which we believe best indicate the status of both the anatomic inflammatory process in the kidneys and the functional disturbances attending the renal lesion. The persistence of the anatomic inflammatory changes in the kidney was gauged by routine urinalyses and Addis urinary sediment counts done frequently. In reporting the results of the Addis sediment count, we have used the values for red blood cell excretion, since we have found these to be the last of the formed urinary "elements" to return to normal. In addition the red blood cell sedimentation rate has been followed in these patients. It is not possible to designate with certainty the factors responsible for the prolongation of the abnormal sedimentation rate in patients with acute glomerulonephritis. The rapid sedimentation rate closely parallels the presence of an abnormal urinary sediment and may conceivably be dependent upon the presence of active inflammatory change in the kidneys. However, the possibility that the continuation of the original focal infection in a subclinical degree not readily apparent, may account for the persistence

of the rapid red blood cell sedimentation rate cannot be excluded. The major functional disturbances resulting from the renal disease are derangements of renal function and functional abnormalities in the cardiovascular system chiefly dependent upon vascular spasm. The functional status of the kidney was measured by both the urea clearance test and the phenol-sulfonphthalein excretion test. The return of the blood pressure to a normal level was taken as an indication of the disappearance of vascular spasm. Frequent clinical, roentgenographic, and electrocardiographic examinations of the heart served as a guide in determining the status of this organ.

8 days in the sulfanilamide treated group and 6 days in the untreated group. The proportion of patients with clinically apparent cardiac involvement was almost the same in both groups, 10 patients or 30% in the sulfanilamide treated group, and 13 patients or 32% in the control group. Similarly there were 20 patients or 60%, with significant hypertension in the sulfanilamide treated group and 23 patients or 57% in the controls. While there is no precise method for expressing quantitatively, the severity of the disease, when the patient is first seen, the overall impression of both groups with respect to the degrees of severity of nephritis on admission to the hospital was that they

TABLE 1.—DATA ON THE TREATED AND UNTREATED GROUPS

	Untreated group	Sulfanilamide treated group
Number in groups	40	33
Average age	6 \pm 3 yrs.	6 \pm 3.1 yrs.
Duration of nephritis before admission to hospital	6 days (1 to 29 days)	8 days (1 to 35 days)
Cardiac involvement (clinically evident)	13	10
Hypertension	23	20

TABLE 2.—ORGANISMS ISOLATED IN THE TWO GROUPS OF PATIENTS

Predominant organism	Untreated group (40)	Sulfanilamide treated group (33)
<i>Streptococcus hemolyticus</i>	24	18
<i>Staphylococcus aureus</i>	10	7
<i>Pneumococcus</i>	2	4
<i>Streptococcus viridans</i>	4	3
<i>Micrococcus catarrhalis</i>	0	1

The two groups of children with acute glomerulonephritis were similar in so many respects that they are comparable samples. About half the children in each group were negroes which is in keeping with the proportion of colored children admitted to the Children's Hospital of Philadelphia for all causes. The average age of both groups was approximately 6 years. In both groups there was a slight preponderance of males—57%. Osman⁵ showed that the preponderance of males affected by this disease is significant in every age group except that from 16 to 20 years. The duration of the disease before admission to the hospital, and thus initiation of treatment, was not appreciably different, averaging

did not differ appreciably. Table 1 summarizes some of the characteristics of both groups of children at the time of admission to the hospital. Both groups of patients were hospitalized continuously until they were judged to be free from their disease. The treatment of all patients other than the administration of sulfanilamide was similar.

Routine nasopharyngeal and blood cultures were taken on all patients at the time of admission to the hospital. In addition cultures of any infected skin lesions or purulent discharges were obtained. Table 2 presents the results of the nasopharyngeal cultures. While many of the patients had a variety of organisms in

their upper respiratory tracts, only the predominant organism is recorded. The beta hemolytic streptococcus was the organism most frequently encountered, 60% of the untreated group and 54% of the sulfanilamide treated group. Unfortunately, repeated cultures were not done, for it is likely that a higher incidence of streptococcal infection would have been revealed in this way. In only 1 instance a patient, who had an antecedent history of scarlet fever was a positive blood culture obtained (beta hemolytic streptococcus). It may be assumed that infection with the beta hemolytic streptococcus was present in many patients from whom the organism was not isolated in culture, since Longcope³ has demonstrated with great

100 cc.—in only 2 patients did the blood concentration exceed 10 mg. per 100 cc. Hemoglobin determinations and white blood cell counts were made every third day for 12 days and at weekly intervals thereafter.

Most of the patients were cyanotic during the first week of therapy. Two patients developed a marked drop in hemoglobin which was treated by blood transfusions without stopping the sulfanilamide. One child developed on the third day of drug administration a weeping cutaneous eruption with involvement of the mouth, conjunctivæ, vagina and perineal region (a type of erythema multiforme which has been termed ectodermosis erosiva pluri-

TABLE 3.—RATES OF RETURN TO NORMAL OF FINDINGS INDICATIVE OF PERSISTENCE OF RENAL LESION

	Untreated group (days)	Sulfanilamide treated group (days)
Routine urinalysis	37 ± 18	32 ± 17
Addis count:		
10,000,000 red cells	76 ± 32	63 ± 29
Less than 1,000,000 red cells	120 ± 75	86 ± 69
Sedimentation rate	86 ± 48	71 ± 46

TABLE 4.—RATES OF RETURN TO NORMAL OF ALTERED PHYSIOLOGIC FUNCTIONS

	Untreated group (days)	Sulfanilamide treated group (days)
Renal function	19	21
Heart	14	10
Blood pressure	7	8.5

regularity a marked rise in the antistreptolysin titer of the blood during the course of acute glomerulonephritis, even when cultures failed to show hemolytic streptococci.

Sulfanilamide was administered orally according to a fixed plan. Every patient received 1 gr. per pound of body weight daily for 5 days, following an initial dose of half the calculated total daily dose. The drug was then administered at half this dosage level for an additional 15 days, and finally a maintenance dose of 10 to 20 gr. daily was given for variable periods of 2 to 6 weeks. Thus sulfanilamide was given over a period of 34 to 62 days. Blood sulfanilamide concentrations measured in 19 patients varied from 4 to 16 mg. per

officialis). No severe leukopenias were encountered.

Other than local therapy for cutaneous infection (impetigo) and myringotomy when indicated, no other attempt at removal of foci of infection was made during the study of both groups of children.

Results. The value of sulfanilamide administration in the treatment of the patient with acute glomerulonephritis may be examined from two aspects, first, its effect on the infectious episode which precedes and presumably precipitates the renal disturbance and, second, the influence upon the course and duration of the renal disease. While physical examinations showed that the original infections were controlled and clinically arrested by

the drug, since serial nasopharyngeal cultures were not done we cannot state when the bacterial infection was terminated. The data accumulated in this study pertain solely to the influence of sulfanilamide upon various manifestations of the diseased kidneys and the duration of the inflammatory process in the kidneys. In Table 3, there are presented the average durations of the abnormalities in routine urinalysis, Addis urinary sediment count, and sedimentation rate for both the sulfanilamide treated and control groups.

The routine urinalysis became normal in both groups in about the same length of time—37 days in the untreated group, and 32 days in the sulfanilamide treated group. The Addis urinary sediment count, reporting excretion of red cells only, seemed to return to normal somewhat sooner in the sulfanilamide treated group, an average of 86 days as opposed to 120 days in the control. However, because of the large values for the standard deviation, this difference is not statistically significant. The red blood cell sedimentation rate returned to normal in 71 days in the sulfanilamide treated group and in 86 days in the untreated group. Again, because of the wide variability in each group, the difference in these two average values has no statistical significance. It seems reasonable to conclude that sulfanilamide administration was without influence on the duration of the inflammatory lesion in the kidney. Complete recovery from acute glomerulonephritis occurred in all patients in both groups.

Serial estimations of renal function by the urea clearance test or phenolsulphonphthalein excretion test or both were made in the 2 groups of patients. Sulfanilamide administration had no influence upon the time required for the restoration of normal kidney function, as measured by these tests, 21 days in the treated group and 19 days in the untreated group (Table 4). This finding may also be regarded as additional evidence that sulfanilamide in therapeutic doses does not depress renal function in these patients.

Since hypertension, which occurred in 60% of all the patients is an important etiologic factor in the serious complications, heart failure and hypertensive encephalopathy, it is of interest to note that the duration of hypertension was not influenced by sulfanilamide administration. The blood pressure attained normal levels in 7 days in the untreated group and 8.5 days in the treated group (Table 4).

Of the entire group of patients, 31% presented evidences of cardiac abnormalities which were apparent on physical examination. The return to a normal cardiac status in these patients was determined by repeated physical, roentgenographic, and electrocardiographic examinations. There was no significant difference in the duration of cardiac abnormality in the 2 groups (Table 4). Thus sulfanilamide therapy did not affect the course of the above mentioned physiologic derangements which so frequently accompany acute glomerulonephritis.

Since acute glomerulonephritis in children in marked contrast to this disease in adults rarely progresses to a chronic stage, it is obvious that the duration of the illness rather than the incidence of chronicity must serve as a criterion in assessing the action of sulfanilamide therapy in childhood. This difference in the natural history of the disease between the child and the adult, may account for the differences in therapeutic results obtained in this study and those reported by Williams *et al.*⁷ The reasons for this difference in the course of acute glomerulonephritis in the child and adult are not apparent and are certainly worthy of further study.

The production of the renal lesion of acute glomerulonephritis generally is believed to result from an allergic reaction in the kidney dependent upon an extrarenal focus of infection. Whether the severity and persistence of the antecedent infection bear any relation to the severity and persistence of the acute renal lesion is not clear. If there were a high degree of correlation between these two processes, then the administration of sulfanilamide

would be expected to decrease the severity and duration of the acute renal episode because of the suppression of the focus of infection. Since sulfanilamide administration did not decrease the severity or duration of the disease in the children studied, it is possible that factors other than original focus of infection may be operative.

Summary and Conclusions. 1. A group of 33 children with acute glomerulonephritis, treated with sulfanilamide was compared to a group of 40 children with the same disease, not given this drug. Both groups were comparable in age, sex, duration of illness prior to hospitalization, severity of renal disturbance, in the incidence of accompanying cardiovascular derangements, and in the predominant infecting organism (the beta hemolytic streptococcus).

2. All children in both groups recovered completely from their renal disease.

3. There was no significant difference in the duration of the renal inflammatory process as estimated by the routine urinalysis, Addis urinary sediment count, and red blood cell sedimentation rate.

4. There was no statistically significant differences between the duration of the disturbed renal or cardiovascular functions in the two groups.

5. Sulfanilamide had no demonstrable deleterious effect on the renal function and did not cause an unusual incidence of toxic phenomena in patients with acute glomerulonephritis.

6. Sulfanilamide therapy appears to be without influence on the course and duration of acute glomerulonephritis in childhood. This does not deny the value of sulfanilamide (and other sulfonamides) in the treatment of infection in the patient with nephritis.

REFERENCES

1. LOEHLEIN, M.: Über die entzündlichen Veränderungen der Glomeruli; der menschlichen Nieren und ihre Bedeutung für die Nephritis, Leipzig, S. Hirzel, 1907.
2. LONGCOPE, W. T.: The Pathogenesis of Glomerular Nephritis, *Bull. Johns Hopkins Hosp.*, **45**, 335, 1929.
3. LONGCOPE, W. T.: Studies of the Variations in the Antistreptolysin Titer of the Blood Serum From Patients With Hemorrhagic Nephritis, *J. Clin. Invest.*, **15**, 268, 277, 1936.
4. MARSHALL, E. K., JR., and EMERSON, K., JR.: The Toxicity of Sulfanilamide, *J. Am. Med. Assn.*, **110**, 252, 1938.
5. OSMAN, A. A.: Studies in Bright's Disease: IV. Some Observations on the Incidence and Diagnosis of the Various Forms of Acute Nephritis With an Analysis of 388 Cases, *Guy's Hosp. Rep.*, **79**, 1, 1929.
6. RUBIN, M. I., RAPOPORT, M., and WALTZ, A. D.: A Comparison of Routine Urinalysis, Addis Count and Blood Sedimentation Rate as Criteria of Activity in Acute Glomerulonephritis, *J. Pediat.*, **20**, 32, 1942.
7. WILLIAMS, R. H., LONGCOPE, W. T., and JANEWAY, C. A.: The Use of Sulfanilamide in the Treatment of Acute Glomerular Nephritis, *Am. J. Med. Sci.*, **203**, 157, 1942.

THE TREATMENT OF TEMPORARY RENAL INSUFFICIENCY (UREMIA) BY PERITONEAL LAVAGE

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EVEN though the syndrome known as uremia occurs fairly frequently and the diagnosis can be made quite readily there is no positive proof as to the cause of death in this condition. As Harrison and Mason¹³ have pointed out, numerous theories have been advanced, and it seems plausible that various factors might lead to death in different patients, or that a combination of factors may be present. Death therefore seems to result from an accumulation of toxic products, changes in the osmotic pressure of the body fluid, dehydration or overhydration, an acid-base imbalance or a combination of one or more of the aforementioned causes.^{9,13}

The primary function of the kidney is to eliminate waste or toxic products (glomerular function) and at the same time maintain a normal electrolyte and water balance (largely dependent on tubular function). Regardless of the cause of uremia it is therefore evident that in treating such a syndrome successfully a normal internal environment must be maintained and all the aforementioned items must be kept in mind. Attempts have been made to treat both experimental animals^{6,11,12} and patients^{19,25} by peritoneal lavage but the results to date have not been too satisfactory, apparently due to the fact that the water and electrolyte balance was not sufficiently considered. It has been emphasized⁶ that such a method should be employed only in cases that have a temporary and severe renal dysfunction. Patients suffering from bichloride of mercury poisoning, or from a toxic nephrosis resulting from the administration of one of the sulfonamide compounds would be good candi-

dates for such therapy providing other measures had failed or were thought to be of no avail. Other possible applications for peritoneal lavage might well be in patients who were anuric following a hemolytic transfusion reaction or a crushing injury. Bywaters⁷ has recently reviewed the literature on the "Crush Syndrome" and states that if anuria occurs the prognosis is grave. Therefore it seems possible that if such patients could be maintained for several days it might provide the necessary time for satisfactory kidney function to be restored. Moon^{16,17} has felt that toxic products accumulate in certain types of shock, and if such is the case, it naturally follows that these toxic products pass through living membranes by dialysis. It therefore seems possible that they too could be eliminated from the body by peritoneal lavage.

In order to clarify the procedure to be used it was first necessary to settle the following points:

1. The method of carrying out peritoneal lavage: (a) continuous perfusion; or (b) intermittent injection and then withdrawal: (1) length of time fluid should remain in peritoneal cavity; (2) method of injection and frequency.

2. The selection of a proper solution with the following qualifications: (a) one which would permit a maximum diffusion of waste products into it; (b) one which would not alter the normal electrolyte pattern of the extracellular fluid; (c) one which would have the desired tonicity, and if possible; (d) a solution which would afford nutrition and thus keep the protein catabolism at a minimum.

With these problems in mind this study was undertaken in order to determine what solution could be best employed. It also seemed important to perfect the method of lavaging the peritoneal cavity so extremely large quantities of fluid would not have to be used and to use a solution which could be completely recovered.

Materials and Method. It was felt that intermittent washings of the peritoneal cavity would cause less difficulty and would be less apt to produce a state of overhydration. It was also thought advisable to use a sterile solution which chemically resembled an ultrafiltrate of plasma. In order to check these impressions it was necessary to establish at what time the maximum diffusion of nitrogenous products occurred and what solution could be best tolerated. Therefore peritoneal lavage employing a 5% solution of dextrose in distilled water, of Ringer's, Hartmann's, and "A" solutions were carried out. The composition of the latter 3 solutions is shown in Table 1.

Normal mongrel dogs were employed for this study and peritoneal lavage was accomplished by injecting the selected fluid through a large gauge needle (No. 15) which had been inserted through the abdominal wall after anesthetizing a small area with 1% procaine. One hundred cc. per kilogram of body weight of the lavage fluid was given intraperitoneally in the first 10 animals. Frequent blood and ascitic fluid samples were taken for analysis at the time interval following injection as shown in Tables 2, 3, 4 and 5.

Following the selection of the method and the solution to be employed ("A" solution) bilaterally nephrectomized dogs were used to further evaluate the procedure. All blood samples except the CO₂ determinations were obtained by employing greased syringes. Samples for the CO₂ content were obtained under oil, and stasis was avoided. Heparin was employed as the anticoagulant for all samples.

The hematocrit was determined by employing the Sanford and Magath cell volume tube.²¹ In the normal animals the plasma protein concentration was calculated from

the plasma specific gravity as advocated by Weech²⁶ employing the falling-drop* method described by Barbour and Hamilton.⁵⁴ In the nephrectomized animals the plasma protein concentration was determined by the micro-Kjeldahl technique and corrected for the elevated non-protein nitrogen. (It was found that the plasma protein concentration as determined chemically did not agree satisfactorily with that calculated from the specific gravity when the blood urea nitrogen was above 100 mg. per 100 cc.) Plasma and ascitic fluid chlorides were determined by employing the modification advocated by Wilson and Ball²⁷ of the method described by Van Slyke.²² The method of Van Slyke and Cullen²³ was employed for the blood and ascitic fluid urea nitrogen and the CO₂ content was determined as described by Van Slyke and Neill.²⁴ In the later experiments 1 kidney was first removed and subsequently after control blood studies had been obtained the remaining nephrectomy was performed in 10 to 15 minutes using a light intratracheal ether anesthesia.

Results. The blood and ascitic fluid alterations noted when 5% dextrose in distilled water was employed for lavage are shown in Table 2. It can be observed that a marked hemoconcentration occurred and that the plasma protein concentration was greatly increased while the plasma chloride concentration fell to very low levels. These changes were due to a shift of electrolytes into the ascitic fluid and water into the intracellular compartment with a resulting dehydration of the extracellular fluid phase. Table 3 shows the changes which occurred when Ringer's solution was used. In these animals only slight alterations were noted in the hematocrit and plasma protein concentration although some dilution apparently occurred. (The plasma chloride level increased slightly while the CO₂ content was decreasing.) The analysis of the ascitic fluid in these dogs (Nos. 3, 4 and 5) showed that considerable amounts of bicarbonate was lost from the extracellular fluid, while chloride (and probably also some sodium)

* Barbour and Hamilton Falling-drop Apparatus kindly furnished by Eimer and Amend & Co., New York, N. Y.

passed from the injected fluid into the extracellular fluid compartment. Tables 4 and 5 show the chemical alterations that occurred when Hartmann's solution and "A" solution (without added dextrose) was employed. It can be seen that very little change in the plasma and ascitic fluid concentrations occurred except for the transfer of urea nitrogen into the lavage fluid. Table 6 shows a summary of these results in the first 10 animals and it is evident that "A" solution and Hartmann's solution would be the most desirable ones to use. Since there is a tendency towards

acidosis in uremia "A" solution was employed in the subsequent experiments because of the greater amount of available bicarbonate.

The blood studies obtained from non-treated bilaterally nephrectomized dogs are shown in Table 7. The average survival time of these animals was slightly over 4 days. All of these dogs showed a high blood urea nitrogen concentration prior to death. Approximately 24 hours after removal of the second kidney in a similar group of animals, peritoneal lavage was instituted. Results in 3 such dogs are

TABLE 1.—SOLUTIONS EMPLOYED FOR PERITONEAL LAVAGE

Solutes in gm. per 1000 cc. of distilled water	Ringer's	Hartmann's	"A" solution
Sodium chloride (gm.)	9.00	6.00	6.10
Calcium chloride (gm.)	0.25	0.20	0.23
Potassium chloride (gm.)	0.30	0.40	0.35
Sodium phosphate (monobasic) (gm.)	0.07
Magnesium chloride (gm.)	0.05
Sodium bicarbonate (gm.)	2.20
Lactic acid (cc.)	2.40	..
Dextrose (gm.)	10-20
Total gm. per 1000 cc.	9.55	..	19-29

TABLE 2.—RESULTS OBTAINED FROM 2 DOGS LAVAGED WITH A SOLUTION OF 5% DEXTROSE IN DISTILLED WATER

Dog No.	Time	Hematocrit	Plasma protein conc. (gm./100 cc.)	Plasma chloride (m.eq./l)	Lavage fluid		
					Urea nitrogen (mg./100 cc.)	Chloride (m.eq./l)	CO ₂ (vol. %)
1	Control	50.0	6.72	113.8	0	0	0
	5 min. after injection				2.1	9.1	3.6
	4 hours	73.0	12.07	86.2	14.1	75.8	23.6
2	Control	49.2	6.12	110.0	0	0	
	2 hours	62.4	8.54	93.8	4.81	44.5	
	3 hours	66.1	9.05	93.6	6.41	53.2	
	4 hours	68.9	9.46	89.9	7.05	59.3	
	6½ hours	78.9	10.44	83.1	9.20	68.1	

TABLE 3.—RESULTS OBTAINED FROM 3 DOGS LAVAGED WITH RINGER'S SOLUTION

Dog No.	Time	Blood and plasma				Lavage fluid		
		Hematocrit	Plasma protein conc. (gm./100 cc.)	Plasma chloride (m.eq./l)	Plasma CO ₂ (vol %)	Urea nitrogen (mg./100 cc.)	Chloride (m.eq./l)	CO ₂ (vol. %)
3	Control	38.5	6.36	109.9	48.2	0*	164.0*	0*
	2 hours	41.0	5.62	116.7	..	11.1	146.2	
	3 hours							
	4 hours	41.6	5.41	117.0	41.7	12.9	135.7	36.5
	5 hours							
	6 hours	44.1	5.41	116.2	..	12.4	130.2	38.2
4	Control	47.2	6.45	112.1	49.4	0*	166.0*	0*
	2 hours							
	3 hours	40.5	5.91	116.9	..	5.8	134.8	
	4 hours	40.0	5.87	119.1	44.1	5.7	133.1	40.6
	5 hours	39.2	5.74	115.2	..	4.5	130.0	
5	Control	49.0	5.58	109.4	44.0	0*	163.0*	0*
	2 hours							
	3 hours	42.2	5.14	112.0	..	9.0	141.2	23.4
	4 hours	41.8	5.17	113.3	41.8	9.3	136.2	29.4
	5 hours	41.3	5.11	118.5	40.2	8.8	131.5	34.6

* The level of the individual constituent in the lavage fluid previous to administration.

shown in Tables 8 and 9. In Dog 11 (Table 8) 1500 to 2500 cc. of "A" solution without dextrose was instilled into the peritoneal cavity two or four times a day and withdrawn 3 to 5 hours later. This was done on the 2d, 4th and 7th days. It can be seen that relatively large amounts of urea nitrogen were removed. In Dog 12 (Table 8) the intermittent intraperitoneal injection and removal of 5000 to 6000 cc.'s

of fluid was done daily. These 2 dogs (Nos. 11 and 12) showed a marked generalized edema by the 5th day following bilateral nephrectomy which increased and appeared to be the cause of death after $8\frac{1}{4}$ and $7\frac{1}{2}$ days respectively. Since fairly large amounts of the injected fluid was not withdrawn it was quite obvious that there was an increase in the animals' body water.

TABLE 4.—RESULTS OBTAINED FROM 2 DOGS LAVAGED WITH HARTMANN'S SOLUTION

Dog No.	Time	Blood and plasma				Lavage fluid	
		Hematocrit	Plasma protein conc. (gm./100 cc.)	Plasma chloride (m.eq./l)	Plasma CO ₂ (vol. %)	Urea nitrogen (mg./100 cc.)	Chloride (m.eq./l)
6	Control	44.2	6.07	112.0	45.2	0*	115.0*
	1 hour	40.5	5.87	111.5	..	4.7	120.0
	2 hours	41.6	5.97	111.5	43.0	6.6	122.3
	3 hours	39.4	5.74	112.4	42.6	7.6	123.2
7	Control	45.1	6.12	110.7	..	0*	110.0*
	1 hour						
	2 hours	44.2	6.09	113.5	..	7.3	121.5
	3 hours						
	4 hours	44.4	6.19	116.3	..	6.8	120.6
	6 hours	43.3	5.99	111.9	..	5.6	119.4

* The level of the individual constituent in the lavage fluid previous to administration.

TABLE 5.—RESULTS OBTAINED FROM 3 DOGS LAVAGED WITH "A" SOLUTION

Dog No.	Time	Blood and plasma				Lavage fluid		
		Hematocrit	Plasma protein conc. (gm./100 cc.)	Plasma chloride (m.eq./l)	Plasma CO ₂ (vol. %)	Urea nitrogen (mg./100 cc.)	Chloride (m.eq./l)	CO ₂ (vol. %)
8†	Control	42.8	5.89	108.5	47.3	0*	113.0*	29.8*
	1 hour	39.8	5.66	108.6	..	4.9	121.8	35.9
	2 hours	38.2	5.58	108.5	46.0	7.2	122.5	41.6
	3 hours	35.8	5.34	110.1	..	7.9	124.8	
9	Control	41.2	6.25	112.7	51.0	0*	114.5*	57.7*
	1 hour							
	2 hours	40.6	6.02	112.6	..	10.7	122.3	60.0
	3 hours	39.1	5.78	113.8	49.2	12.0	123.5	55.3
	4 hours	39.3	5.81	113.0	49.6	11.6	123.5	56.7
10	Control	51.9	6.13	107.2	49.9	0*	119.5	43.3*
	1 hour							
	2 hours	53.0	6.30	108.6	45.0	9.0	121.0	50.8
	3 hours	52.3	6.23	109.2	48.3	9.8	123.0	53.4
	4 hours	50.2	6.04	109.6	50.1	9.2	121.4	51.2

* The level of the individual constituent in the lavage fluid previous to administration.

† In Dog 8 only 1.1 gm. of "A" solution was used in the lavage fluid, instead of 2.2 gm./1000 cc.

TABLE 6.—AVERAGE CHANGE OF THE CONSTITUENTS MEASURED IN THE BLOOD, PLASMA AND LAVAGE FLUIDS AFTER 4 HOURS FOR EACH OF THE SOLUTIONS EMPLOYED

Solution employed	Blood and plasma				Lavage fluid		
	% change in hematocrit	% change in plasma protein conc.	% change in plasma chloride conc.	% change in plasma CO ₂	Increase in urea nitrogen conc. (mg./100 cc.)	M.eq./l change in chloride conc.	Vol. % change in CO ₂ content
5% dextrose in distilled water	+43.1	+67.1	-21.3	..	+10.6	+67.6	+23.6
Ringer's	-7.4	-10.4	+5.5	-9.7	+9.3	-29.3	+35.5
Hartmann's*	-7.4	-2.2	+2.7	-4.9	+7.2	+8.8	
"A" solution†	-4.0	-4.3	+1.3	-1.2	+10.4	+4.7	+8.1

* These values represent the average change (% or conc.) at the end of 3 hours in 1 animal and 4 hours in the other.

† Dog 1, Table 5 omitted from this calculation because only half the intended amount of sodium bicarbonate was used in the solution.

The results with Dog 13 are shown in Table 9. The "A" solution was made slightly hypertonic by the addition of dextrose (the chemical make-up of the fluid was comparable to that shown in Table 1). By such a procedure it is possible to withdraw slightly more fluid than had been injected and thus it was feasible to utilize parenteral fluids to help control the acid-base balance and the state of

nutrition. Nine days following bilateral nephrectomy the animal appeared perfectly normal (no visible edema was evident), and the blood studies were within the desired range. In the evening of the 9th day the dog died suddenly following a transfusion of citrated blood. The caloric and protein intake was maintained fairly well by the dextrose present in the peritoneal fluid and by the administration of

TABLE 7.—BLOOD STUDIES ON BILATERALLY NEPHRECTOMIZED UNTREATED ANIMALS*

Dog No.	Time (in days)	Hematocrit	Plasma protein conc. (gm./100 cc.)	Plasma chloride (m.eq./l.)	Plasma CO ₂ (vol.%)	Blood urea nitrogen (mg./100 cc.)
1	Control	52.0	6.72	110.6	45.3	12.9
	2	45.0	6.47	94.6	41.4	143.7
	4	41.0	6.28	72.2	36.0	256.0
2	Control	45.1	6.12	110.7	49.4	9.0
	1	31.0	5.89	115.3	38.1	61.2
	2	29.2	5.60	107.1	32.7	104.1
	4	28.1	5.50	100.9	51.0	254.0
	5	29.7	5.23	99.4	43.4	299.6
3	Control	43.6	7.55	109.1	48.0	7.7
	2	39.8	..	97.0	46.9	80.8
	3	42.3	6.80	78.0	..	240.0
4	Control	53.8	9.3
	2	39.5	116.0
	4	28.1	190.0

* Average survival time of entire control group of non-treated animals, 4+ days.

TABLE 8.—BLOOD STUDIES ON BILATERALLY NEPHRECTOMIZED ANIMALS TREATED BY PERITONEAL LAVAGE*

Dog No.	Time in days after bilateral nephrectomy	Hematocrit	Plasma protein conc. (gm/100 cc.)	Plasma chloride (m.eq./l.)	Plasma CO ₂ content (vol. %)	Blood urea nitrogen (mg./100 cc.)
11	Control	51.0	6.24	108.4	46.0	10.0
	2 { A.M.	43.0	5.58	106.9	43.3	138.6
	2 { P.M.	46.0	6.70	..	42.6	70.1†
	4	39.0	5.84	106.3	41.6	111.8
	7	41.3	..	100.2	40.7	200.7
	8	45.4	5.62	128.2	38.5	101.1‡
12	Control§	38.5	6.36	109.9	45.2	12.2
	Control¶	43.4	6.25	108.7	54.0	9.1
	1 { A.M.	39.6	..	107.3	..	30.7
	1 { P.M.	26.1
	2	38.3	..	100.7	55.5	35.0
	4 { A.M.	..	4.38	99.0	50.4	38.7
	4 { P.M.	30.7
	5	31.6	..	100.2	50.0	35.4
	7	31.3	4.24	103.0	42.4	63.9

* All blood studies drawn in the A.M. except those so designated.
† 6055 cc. lavage fluid removed during the previous 12 hours containing 5.34 gm. of urea nitrogen.
‡ 7600 cc. lavage fluid removed in the previous 6 hours containing 10.1 gm. of urea nitrogen.
§ Control studies before nephrectomy.
¶ Blood studies following unilateral nephrectomy.

TABLE 9.—DAILY STUDIES ON DOG 13 AFTER BILATERAL NEPHRECTOMY AND TREATMENT BY PERITONEAL LAVAGE

Days of experiment	Control	2	3	4	5	6	7	8	9
Oral or intravenous intake in cc.	100	300	50	750	750	..	550	..
Fluid injected intraperitoneally, cc.	6050	6500	5000	5000	10,000	7500	7800	7900
Fluid withdrawn from peritoneum in cc.	6300	7300	5000	4300	10,000	7925	7800	8200
Serum CO ₂ content, vol. %	47.0	48.1	46.8	42.9	47.0	44.7	41.6	..
Serum chloride, m.eq. per liter	109.2	118.8	104.2	95.5	95.5	98.0	96.3	100.1	101.2
Serum protein conc., gm. per 100 cc.	6.82	6.55
Hematocrit	44.3	43.7	47.0	52.0	57.7	50.0	46.0
Blood urea nitrogen, mg. per 100 cc.	10.3	71.1	73.5	60.0	73.1	86.0	58.0	62.2	54.3

plasma, amino acids and dextrose solutions intravenously. No solid food or water was permitted orally, but the animal was given small amounts of milk on several occasions.

In none of the animals was there evidence of peritonitis. The bilaterally nephrectomized dogs were all autopsied and no abnormalities in the peritoneal cavity were noted.

Discussion. The factors which lead to death when kidney failure occurs can apparently be corrected or prevented by employing peritoneal lavage, but naturally this type of therapy would only be effective over short periods of time (2 to 14 days) and the ultimate success would then depend on the restoration of adequate kidney function.

Ganter¹¹ in 1923 first introduced peritoneal lavage for the treatment of uremia. Previously it had been shown by Putnam¹⁸ that the organic solutes (urea, creatinine, etc.) and the body electrolytes would dialyze across the peritoneal membrane. With this fact in mind Ganter, employing a physiologic solution of sodium chloride, showed improvement in dogs manifesting the uremic state. In 1927 Heusser and Werder¹⁴ employed Ringer's solution and in summary concluded that the best results should be obtained by using a lavage fluid which approached the normal electrolyte composition of plasma. In 1932 Bliss, Kastler and Nadler⁶ reported their results and showed that as much as 9.9 gm. of non-protein nitrogen could be removed from uremic dogs in less than 24 hours. In their series, untreated bilaterally nephrectomized dogs survived approximately 3 days while in two similar animals in which the peritoneal cavity was lavaged, life was maintained for 13 and 16 days. They used a solution of balanced salts and allowed it to remain in the peritoneal cavity for 10 minutes before removal. The cause of death in some of the animals which they treated was apparently due to the accumulation of massive peripheral and pulmonary edema. In the lavage fluid after removal they identified creatinine, urea, phosphates, sulphates, urochrome

and traces of protein. Haam and Fine¹² were able to reduce significantly the mortality rate by employing peritoneal lavage in rabbits which were made anuric by administering 30 mg. of bichloride of mercury per kilogram of body weight. Wear, Sisk and Trinkle²⁵ in 1938 employed this method of treatment, experimentally and clinically, using a poorly buffered Hartmann's solution with a pH of 4.2. Their results showed promise inasmuch as they also demonstrated that large quantities of non-protein nitrogen could be removed. They believed the procedure was without morbidity or mortality, and emphasized the fact that it would be successful only if acidosis could be prevented. Most of the investigators who have employed this procedure have used solutions which were not comparable to plasma in composition, and as a rule perfused the peritoneal cavity by inserting two trochars or rubber catheters. Haam and Fine¹² on the other hand inserted the fluid, which was kept at body temperature, intraperitoneally through a small rubber catheter and then after 10 to 30 minutes removed it by syphonage. It was noteworthy that the lavage fluid attained a relatively high urea nitrogen concentration although the average length of time between injection and withdrawal was less than 30 minutes.

The procedure has been employed in at least 13 human cases^{6,14,19,20,25} with one reported survival.²⁵ In most instances a definite reduction in the blood urea nitrogen concentration was obtained. The failures were thought to occur because of the existence of permanently diseased kidneys in most of the cases, and occasionally it was thought to be due to inadequate or incorrect treatment.

Although the series of animals presented here is small, it is believed that certain definite knowledge was gained which would permit the wider use of this method.

That dialyzation of large quantities of urea nitrogen into the lavage fluid will occur has been demonstrated (up to 10.1 gm. of urea nitrogen was removed in 16 hours). Our studies and those of others^{6,6,7}

have shown that the normal daily output of urea nitrogen can be approximated or exceeded by the use of peritoneal lavage. It is appreciated that the symptoms of uremia are not a result of the high concentration of urea nitrogen when kidney function is impaired. It has been shown^{9,10,13} that toxic products are formed, and that there is also a retention of protein breakdown products.¹³ If such be the case since such products are dialyzable^{6,11,18} it seems logical to assume that uremic patients can be benefited by peritoneal lavage. In our experiments the urea nitrogen concentration was taken as a relative index of the rate and quantity of dialyzation of such products.

The maximum diffusion of urea nitrogen into the lavage fluid apparently occurs in from 2 to 4 hours. Haam and Fine¹² and Rhoads¹⁹ demonstrated a more rapid rate of diffusion when the blood urea nitrogen was significantly elevated. It thus seems that it is more desirable to employ the intermittent injection and withdrawal ($\frac{1}{2}$ to 4 hours) technique rather than a continuous perfusion.

It has been previously demonstrated^{8,15} that a 5% dextrose solution causes many undesirable alterations and hence would not be a suitable lavage fluid although it was employed in some of the experiments done by Rosenak and Simon.²⁰ Ringer's solution would not be satisfactory because of the lack of bicarbonate and its high chloride concentration. The repeated lavaging with such a solution would result in a considerable loss of bicarbonate from the blood.

With the use of any of the isotonic salt solutions a retention of sodium and hence water is apt to occur and result in extreme overhydration and pulmonary edema. This has also been observed by others;⁶ therefore we feel that by the addition of small amounts of dextrose, the lavage fluid is made slightly hypertonic and complete recovery of the injected fluid can be obtained. In fact, it is possible to withdraw somewhat larger quantities, thus permitting the use of oral feedings or solu-

tions intravenously which contain constituents needed to maintain adequate nutrition (vitamins, amino acids, dextrose and electrolytes). It would seem quite desirable to provide an adequate carbohydrate intake so that the catabolism of body proteins would be reduced and the accumulation of organic acids could be kept at a minimum. Other investigators^{6,19} have shown that a decrease in the blood sugar concentration and a rise in the concentration of glucose in the lavage fluid occurs if glucose is not present in the lavage fluid. This could be easily prevented by giving adequate amounts of dextrose.

The results obtained in the control dogs with Hartmann's and "A" solution were essentially comparable in regard to the status of the fluid and acid-base balance. Certain advantages, however, may be accredited to "A" solution, namely, (1) it supplies more of the electrolytes commonly found in plasma than does Hartmann's solution, and (2) there is more bicarbonate available in the "A" solution.

The question of whether hormones were lost by such a procedure was considered, but since we have no information on this no positive statements can be made. It is felt, however, that animals and patients could probably combat the moderate deficits that might result.

Summary. From our studies and from previous work^{6,11,12,19,25} it would seem that peritoneal lavage if properly employed for the treatment of uremia (and possibly other toxemias) could be an advantageous procedure.

It seems desirable to use the intermittent injection and withdrawal of a solution which has a chemical composition similar to that of interstitial fluid and is made slightly hypertonic by the addition of small amounts of dextrose (or gelatin or pectin). It would be essential to follow the acid-base balance closely by fairly frequent chemical determinations (total base, CO₂ content, plasma chloride level and pH), and in the event the procedure was carried out for any length of time, it would seem important to administer small

amounts of whole blood occasionally to prevent a marked depletion in the red blood cell and plasma protein concentration. If the electrolyte composition of the blood became abnormal it would be desirable to alter the composition of the lavage fluid as advocated by Rhoads¹⁹ in order to remove solutes which were present in excess or provide ones which were decreased.

As has been emphasized previously^{1,2,3,15} the hematocrit, hemoglobin, red blood cell count and plasma protein concentration would not provide reliable indices of an anemia or hypoproteinemia. Neither such studies nor the plasma electrolyte concentrations would be of much value in determining quantitatively the patient's state of hydration. The former problems could be controlled by the giving of an

adequate diet or transfusions, while the latter could best be judged by careful and frequent observations of the patient, and the keeping of accurate intake and output records.

Conclusions. 1. In control animals urea nitrogen will diffuse quite rapidly into fluid which has been injected intraperitoneally.

2. A solution which has a chemical make-up similar to interstitial fluid would be suitable for lavaging the peritoneal cavity and would not greatly alter the state of hydration* or the acid-base balance.

3. Relatively large amounts of nitrogenous waste products and presumably other toxic elements can be removed from dogs by peritoneal lavage, keeping nephrectomized animals in relatively normal state for over a week.

The authors wish to acknowledge the help and advice which was so generously given by Drs. V. C. Myers, E. Muntwyler, A. Free, G. E. Gustafson and J. Leonard of the Department of Biochemistry, and to Dr. C. H. Lenhart of the Department of Surgery and Dr. Max Miller of the Department of Medicine of Western Reserve University School of Medicine for their encouragement in undertaking this work and their helpful suggestions in the preparation of the manuscript.

REFERENCES

1. ABBOTT, W. E., and MELLORS, R. C.: *Arch. Surg.*, **46**, 277, 1943.
2. ABBOTT, W. E., MELLORS, R. C., and MUNTWYLER, E.: *Ann. Surg.*, **117**, 39, 1943.
3. ABBOTT, W. E., MEYER, F. L., HIRSCHFELD, J. W., and GRIFFIN, G. E.: *Surgery* (in press).
4. BALAZS, J., and ROSENAK, S.: *Wien. klin. Wchnschr.*, **47**, 851, 1934.
5. BARBOUR, H. G., and HAMILTON, W. F.: *J. Am. Med. Assn.*, **88**, 91, 1927.
6. BLISS, S., KASTLER, A. O., and NADLER, S. B.: *Proc. Soc. Exp. Biol. and Med.*, **29**, 1078, 1932.
7. BYWATERS, E. G. L.: *J. Am. Med. Assn.*, **124**, 1103, 1944.
8. DARROW, D. C., and YANNET, H.: *J. Clin. Invest.*, **14**, 266, 1935.
9. FISHBERG, A. M.: *Hypertension and Nephritis*, 4th ed., Philadelphia, Lea & Febiger, 1939.
10. GAMO, Y.: *J. Biol. Chem.*, **18**, 457, 1933.
11. GANTER, G.: *München. med. Wchnschr.*, **70**, 1478, 1923.
12. HAAM, E. v., and FINE, A.: *Proc. Soc. Exp. Biol. and Med.*, **30**, 396, 1932.
13. HARRISON, T. R., and MASON, M. F.: *Medicine*, **16**, 1, 1937.
14. HEUSSER, H., and WERDER, H.: *Beitr. z. klin. Chir.*, **14**, 38, 1927.
15. MELLORS, R. C., MUNTWYLER, E., MAUTZ, F. R., and ABBOTT, W. E.: *J. Biol. Chem.*, **144**, 785, 1942.
16. MOON, V. H.: *Am. J. Clin. Path.*, **11**, 361, 1941.
17. MOON, V. H.: *Arch. Path.*, **22**, 325, 1936.
18. PUTNAM, T. J.: *Am. J. Physiol.*, **63**, 548, 1923.
19. RHOADS, J. E.: *Am. J. Med. Sci.*, **196**, 642, 1938.
20. ROSENAK, S., and SIWON, P.: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, **39**, 391, 1926.
21. SANFORD, A. H., and MAGATH, T. B.: *J. Lab. and Clin. Med.*, **15**, 172, 1929.
22. VAN SLYKE, D. D.: *J. Biol. Chem.*, **58**, 523, 1923.
23. VAN SLYKE, D. D., and CULLEN, G. E.: *J. Biol. Chem.*, **24**, 117, 1916.
24. VAN SLYKE, D. D., and NEILL, J. M.: *J. Biol. Chem.*, **61**, 523, 1924.
25. WEAR, J. B., SISK, I. R., and TRINKLE, A. J.: *J. Urol.*, **39**, 53, 1938.
26. WEECH, A. A., REEVES, E. B., and GOETTSCH, E.: *J. Biol. Chem.*, **113**, 167, 1936.
27. WILSON, D. W., and BALL, E. G.: *J. Biol. Chem.*, **79**, 221, 1928.

* In several human cases which were in a terminal state, the injection and withdrawal of such a solution has been tried. Although our experience in human patients is very limited, it would appear that the withdrawal of the fluid could be best accomplished by the use of a trochar or insertion of a rubber catheter, since the insertion of a needle does not, as a rule, permit a complete recovery of the injected fluid.

RELATIVE EFFICIENCY OF QUINACRINE (ATABRINE) AND QUININE IN TREATMENT OF ACUTE ATTACKS OF VIVAX MALARIA

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PRIOR to the introduction of quinacrine (atabrine) for the treatment of malaria, the medical profession and the public had, for centuries, accepted quinine without question as the best available drug for the treatment of malaria.

Quinacrine was introduced as a new anti-malarial drug in 1931 and was said to be effective in controlling acute attacks of malaria in 5 days during which time a total of 1.5 gm. had been administered by mouth. Early clinical trials in the field proved its value although it soon became apparent that the originally advocated regimen of 0.1 gm. three times daily for 5 days would have to be revised upwards so that not only would the total dose be greater but the amount given the first day also considerably increased, for prompt control of fever and symptoms especially in falciparum infections.

The curtailed supply of quinine as a result of war developments placed the major burden of malaria therapy on quinacrine. Extensive coöperative studies by military and civilian research groups on the pharmacology of quinacrine led to a more rational understanding of the relation of drug dosage, plasma level, and effectiveness in the treatment of acute attacks of malaria as well as clinical suppression. As a result of these studies specific recommendations for its use have been adopted with success by the military forces.

Nevertheless, the civilian medical profession has been reluctant to accept quinacrine freely and in many instances it has been prescribed grudgingly only because quinine was not available. Numerous allegations of poor results are known for

the most part to be the result of improper dosage.

The purpose of this paper is to present a comparison of the relative efficiency of quinine and quinacrine in the treatment of acute attacks of vivax malaria.

Treatment Schedules. A. *Quinacrine.* Three hundred and ninety-seven consecutive patients with acute clinical attacks of vivax malaria with fever and parasitemia were treated with quinacrine as follows: All treatment for purposes of uniformity was begun on the morning following the onset of the current attack. On this day referred to as Day 1 quinacrine dihydrochloride 4 tablets = 0.4 gm. was given after breakfast, 3 tablets = 0.3 gm. after lunch and 3 tablets = 0.3 gm. after supper making a total of 10 tablets or 1 gm. on the 1st day. On days 2 to 7 inclusive, 1 tablet of 0.1 gm. was given 3 times daily after meals so that a full course consists of 2.8 gm. during 7 days of therapy. Parasite counts were done twice daily and continued until negative for 3 consecutive days. Plasma quinacrine levels were determined on the 2d and 8th days. Clinical response was followed by daily rounds at which time all signs and symptoms possibly related to malaria or quinacrine were entered on special study forms. The patients left the wards on the 8th day and 200 of them were followed at a convalescent and reconditioning area for 120 days or until relapse. During this interval smears were examined twice weekly and in the event of parasitemia the temperature was recorded 4 times daily until the next smear. A temperature rise of over 100° F. by mouth associated with a positive smear was considered a relapse and the patient was readmitted to a ward for further observation and retreatment.

B. *Quinine.* One hundred consecutive clinical attacks of vivax malaria were treated

with quinine as follows: As with the quinacrine group, all treatment was started on the morning after the onset of the current attack. On Day 1, quinine sulphate in disintegrating tablets was given at exactly 3-hour intervals. Each dose was 1 gm. so that 3 gm. were administered on the 1st day. On Days 2 to 14 inclusive, 0.65 gm. were given 3 times daily at 8-hour intervals so that a total of 2 gm. were administered daily for each of the 13 days. Thus, a course of treatment consisted of the administration of 29 gm. of quinine sulphate during 14 days. Parasite counts were done twice daily until negative in thick drops for 3 consecutive days. Minimum and maximum plasma

Results. A. Control of Parasitemia. The rate of disappearance of parasites from the peripheral blood during administration of quinacrine and quinine, and their relative efficiency in this respect is shown in Chart 1. Within 12 hours after the first dose of quinacrine some patients already had negative smears. This did not occur with quinine. At 24 hours, 26% of patients receiving quinacrine were parasite free, but only 7% receiving quinine. At 48 hours the percentages were 77 and 44, respectively. At 72 hours only 4% of patients receiving quinacrine still

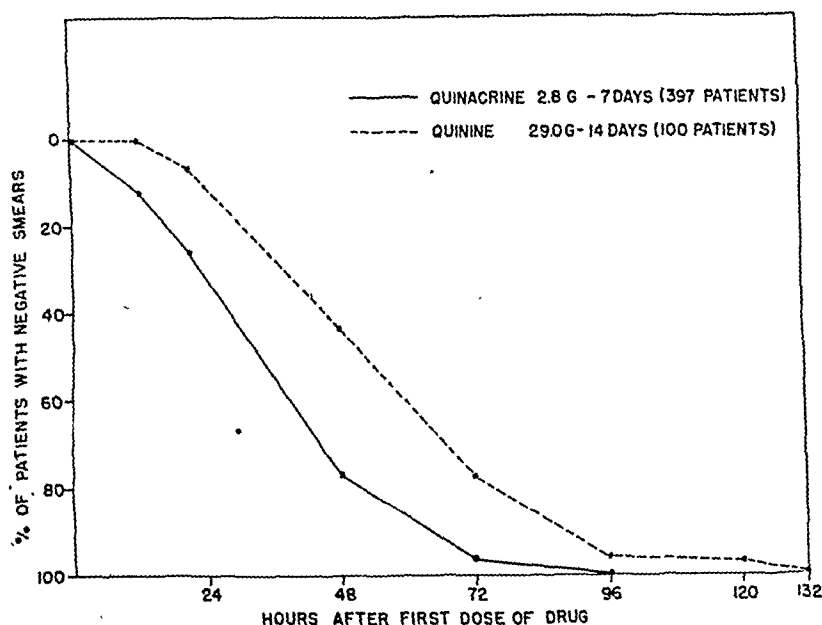


CHART 1.—Rate of disappearance of parasites during treatment of 497 acute attacks of vivax malaria with quinacrine or quinine.

quinine determinations were performed on specimens obtained on the 2d, 7th, and 14th days of treatment. Clinical response was determined by daily rounds at which time all signs and symptoms possibly related to malaria or quinine were recorded on special study forms. The patients left the wards on the 15th day and were followed in a convalescent area for 120 days or to clinical relapse. In the interval, smears were examined twice weekly and in the event of parasitemic relapse the patient's temperature was recorded 4 times daily until the next smear. If a rise over 100° F. by mouth occurred associated with a positive smear the patient was admitted to the wards as a clinical relapse for retreatment and study.

showed parasites, and all were clear at 96 hours. With quinine, on the other hand, almost one-fourth still had parasitemia, and in a few, this persisted as long as 132 hours. Thus, in rapidly clearing the peripheral blood of malarial parasites, quinacrine is obviously significantly superior to quinine.

B. Control of Fever. Of the quinacrine treated patients, 7% had a temperature of 100.2° F. by mouth or higher on the 2d or 3d days of treatment, and 10% of the quinine treated group had fever using the same criteria. While there is no significant difference between both drugs in their

effectiveness in controlling fever, the contention frequently advanced that quinine should be used for treatment during the first few days of an acute attack because of its superiority in controlling fever quickly is not borne out in this study. Further, in the treatment of delayed primary attacks of vivax malaria, 32% of patients who received quinine had fever on the 2d or 3d days after the beginning of treatment, while only 16% of delayed primary attacks treated with quinacrine had fever on the 2d day or subsequently after treatment was begun. Thus, quinacrine is more effective than quinine in controlling the fever of a delayed primary attack and is just as effective as quinine in controlling the fever of relapses.

C. Control of Symptoms. It is difficult to evaluate data on such symptoms as headache, backache, nausea, malaise, and weakness which are usually present for a few days in a treated attack of malaria in relation to the effect of any drug therapy in controlling them. Statistically there is little difference in the duration of these symptoms during treatment with quinine or quinacrine. However, one gains the clinical impression that these symptoms, particularly the weakness, are more strikingly and more promptly controlled during treatment with quinacrine than with quinine. The patients are anxious to get out of bed sooner, leave less food on their trays, and complain less of weakness or other symptoms during treatment with quinacrine than those receiving quinine. The latter remain in bed longer, seem more apathetic, and eat poorly in comparison to the quinacrine treated patients. Vomiting, abdominal pain and abdominal tenderness are controlled equally well with either drug.

On the whole it is the feeling of all the ward officers concerned in the management of these patients that quinacrine is more effective in promptly controlling the symptoms of an acute attack of malaria than quinine.

D. Toxicity. No major toxic manifestations were encountered during the ad-

ministration of quinacrine. Patients who were reluctant to take quinacrine because of alleged previous intolerance were given the drug in colored capsules without their knowledge of the contents and responded well without symptoms of any kind. Persistent vomiting associated with the malaria attack was controlled by withholding fluids and food by mouth and by intravenous glucose prior to the administration of quinacrine. When the drug was given after several hours freedom from vomiting, this did not recur.

Central nervous system signs or symptoms were not encountered in relation to quinacrine therapy in this series. Two patients with severe eczematoid dermatitis suffered a flare up of their skin disease during quinacrine therapy. However, several patients with eczematoid dermatitis and acute malaria not receiving specific antimalarial therapy likewise had flare ups of the skin process and many others with eczematoid dermatitis and malaria suffered no ill effects from quinacrine. Nevertheless, it is our belief that patients with eczematoid or exfoliative dermatitis and acute malaria should not receive quinacrine if they have had this drug before.

Gastrointestinal symptoms controlled as previously described were not aggravated by quinine. Patients with eczematoid or exfoliative dermatitis and malaria had no activation of the skin process attributable to quinine. One patient receiving quinine developed acute thrombopenia, purpura, and severe angioneurotic edema of the face on the first day of treatment. This patient was subsequently found to be extremely hypersensitive to quinine. Such a reaction though not unknown is admittedly very uncommon. A fairly high proportion of the quinine treated patients complained of severe and annoying tinnitus, buzzing, and fullness in the ears or head. In many instances this seemed to retard prompt and full recovery from the symptoms of the acute attack.

On the basis of possible toxicity related

to quinacrine or quinine the only points in favor of either drug are the absence of tinnitus with quinacrine. With either drug rare cases of idiosyncrasy or sensitization may be encountered.

E. *Effect on Relapse Rate and Interval to Relapse After Treatment.* Approximately 80% of Pacific infections relapsed within the period of observation of 120 days, whether treated with quinacrine or quinine. Thus, neither drug has any advantage with regard to the subsequent relapse rate as measured by 4 months' observation.

occur during the first 30 days and none in less than 21 days. At the end of a month only 9% of the treated patients relapsed compared to 55% of the quinine treated patients. At 40 days the relapses are 25% and 67%, respectively, for quinacrine and quinine. In other words at 40 days, 87% of the patients finally observed to relapse after quinine have done so while only 30% of those finally observed to relapse after quinacrine have done so in the first 40 days after treatment. At 60 days the maximum observed relapse

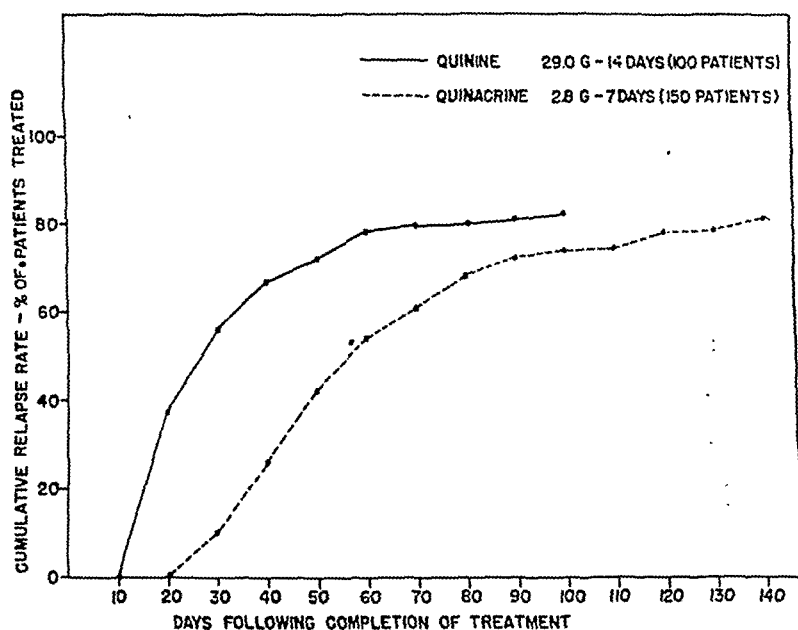


CHART 2.—Relapse rates and intervals to relapse following treatment with quinacrine or quinine of 250 acute attacks of vivax malaria of Pacific origin.

On the other hand there is a striking difference in the interval to relapse following treatment of acute attacks of vivax malaria with quinacrine or quinine. The cumulative relapse rates of the patients treated and observed to relapse or for 120 days as well as the interval to relapse is shown for both drugs in Chart 2.

Relapses following treatment with quinine begin as early as 12 days after completion of treatment and occur frequently during the first 30 days so that at the end of a month 55% of the entire group have relapsed. On the other hand following treatment with quinacrine, few relapses

rate of 80% in the quinine treated group has been reached, whereas following quinacrine the maximum observed relapse rate of 80% was not closely approached until 90 days and not actually reached until 120 days. This means that 30% of the observed relapses after quinacrine occurred after 60 days, while practically no relapses were observed later than 60 days after quinine. The mean interval to relapse following quinacrine is 53 days compared to 22 days following quinine.

Since neither drug materially influences the relapse rate, it is desirable to select a regimen which produces the longest pos-

sible interval to relapse. In this respect quinacrine is obviously very much better than quinine not only in effecting a longer interval to relapse by at least a month, reducing to a minimum relapses within 30 days, and providing in at least 30 % of relapses an interval longer than 60 days.

Conclusions. 1. Quinacrine is superior to quinine in the treatment of acute attacks of vivax malaria for the following reasons: (a) More prompt and effective

control of parasitemia and symptoms; (b) decidedly longer interval to relapse following completion of treatment; (c) absence of disturbing symptoms of cinchonism.

2. Quinacrine given according to the dosage plan described is more effective than quinine in controlling the fever of delayed primary attacks and is as effective in promptly controlling fever in relapses.

QUALITATIVE CHANGES IN FIBRINOGEN WHICH INFLUENCE THE ERYTHROCYTE SEDIMENTATION RATE AND THE CLOT RETRACTION TIME

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THE work reported in this communication was carried out in an effort to find the ingredient or property inherent in plasma responsible for its ability to determine the blood sedimentation rate.

The blood sedimentation rate is essentially an expression of the degree of erythrocyte rouleau formation or clumping. Large clumps of cells will fall more rapidly than smaller ones. Although the aggregates are not spherical, Stokes' Law of Hydrodynamics, which deals with the rate of fall of spherical bodies in a liquid, depending upon their diameter, roughly applies.¹ If the actual process of sedimentation of blood in a hemocytometer is watched through a microscope tipped to a horizontal position, the large clumps of cells will be seen to fall rapidly, the single erythrocytes will fall slowly and at practically the same rate regardless of the sedimentation rate of that particular specimen of blood plasma, unless their speed is temporarily altered by eddy currents such as are produced by nearby rapidly falling clumps of cells.

Blood sedimentation rates are due to constituents of, or properties inherent in, plasma.¹ The erythrocytes play merely a passive rôle. Considerable investigation has been carried out in an effort to determine why two different plasmas of practically identical physical and chemical characteristics should cause widely different erythrocyte sedimentation rates. The yield of factual results has not been great.

If blood is deprived of its fibrinogen by clotting, the resulting serum will have lost whatever ability the plasma had to produce erythrocyte rouleau formation. This fact indicates that fibrinogen is the ingredient in blood that determines the erythrocyte sedimentation rate. Investigators have failed, however, to demonstrate any

consistent relationship between the concentration of blood fibrinogen and the blood sedimentation rate. In these investigations, fibrinogen was presumed to be of the same composition in all bloods.

The ingredient in plasma sought for was found to migrate to the positive pole when plasma was subjected to an external field of electrical force. It failed to pass through a semi-permeable membrane, such as cellophane interposed in the field. These findings point to a large negatively charged molecule as the ingredient sought; any of the blood proteins may answer this description.

Fibrinogen of plasma samples was extracted by the common salting-out technique and redissolved in physiologic saline solution. Washed erythrocytes were found to manifest essentially the same degree of stability in these fibrinogen solutions as they did in the blood plasmas from which the fibrinogen samples were extracted. This finding more definitely points to fibrinogen as the constituent of plasma that determines the blood sedimentation rate. Although such evidence is confirmatory, it is not conclusive. Therefore, it was decided to find and study a simpler suspensoid which might simulate the blood sedimentation reaction. It was thought that examination of such a suspensoid might reveal facts that would lead to a more thorough understanding of the blood sedimentation reaction. An outline of the steps taken in the work that led to the opinions herein submitted may be of interest.

Procedure. A suspension of washed cells of commercial compressed yeast in a colloidal solution of gelatin was found to be a simple mixture that could be made to mimic the blood sedimentation reaction. The hemagglutination of erythrocytes by gelatin was

described in 1920 by Karsner and Hanzlik.⁴ An increase in the blood sedimentation velocity following the intravenous use of gelatin solutions therapeutically has been reported.⁷

Blood sedimentation velocities were simulated by packed cell volumes of 10 to 33% yeast cells in 0.25 to 5% aqueous solutions of gelatin. The rate could be diminished by diluting the suspensoid with water. It could be accelerated by increasing the temperature of the solution or by tipping the containing test tube from the perpendicular, as is the case when sedimenting blood is subjected to these influences.⁶ The yeast sedimentation rate could be rechecked after shaking the tube enough to resuspend the cells. The possibility of specific gravity being an important factor in the process was discredited in light of the fact that the addition of gelatin to water increases its specific gravity, but also increases the solution's ability to produce a rapid sedimentation of yeast cells.

Yeast cells lend themselves well to this type of experimental work, because they are able to withstand relatively wide excursions of osmotic pressure, temperature, and pH changes. Sedimentation rates of yeast cells in plasma samples were slightly slower than, but paralleled those of erythrocytes. The yeast used was commercial compressed yeast or *Saccharomyces Cerevisial* Hansen.⁵ The cells have a density of approximately 1.0 to 1.1; they are oval in shape, and quite variable in size, measuring from 5 to 7 microns on the short axis, and from 7 to 9 microns on the long axis. They carry a negative electric charge in aqueous suspension. Red blood cells carry a negative charge in plasma.¹

In the first series of experiments, solutions of commercial gelatin were used as the dispersing phase. The degree of sedimentation of yeast cells or erythrocytes was found to be directly proportional to the concentration of gelatin in the suspending solution, up to about 5%. Greater concentrations of gelatin were too viscous, and jelled too rapidly to be tested.

Commercial gelatin is commonly a mixture of two types of gelatin.⁸ One type is prepared from an acid-treated precursor, to yield a gelatin positively charged in aqueous solutions, its pH is about 4.0, its isoelectric point is pH 7.8 to 9.3. The second type is prepared from an alkaline-treated precursor, to yield a gelatin negatively charged in

aqueous solutions. Its pH is about 6.0, its isoelectric point is approximately 4.7. The hydrophilic properties of both of these gelatins are dependent on pH, and also the pH in relation to the isoelectric point. For instance, the first type shows a minimum water absorption at pH 8.0, and its ability to absorb water increases on either side of this point. The second type shows a minimum water absorption at pH 4.7, and its ability to absorb water increases with changes away from this, its isoelectric point. Samples of each of these two types of gelatin were secured from a reliable concern.

Yeast cells sediment rapidly in aqueous solutions of negatively charged gelatin, but very slowly in aqueous solutions of positively charged gelatin (Fig. 1). The same reaction was noted when erythrocytes were substituted for yeast cells, and physiologic saline for water (Fig. 2).

The difference in sedimentation velocity of the cells in the two gelatin solutions was at first thought to be due to the difference in electrical charge carried by the gelatin. Further experimentation proved that the pH of the solution, rather than the type of charge carried by the colloid, was responsible for the difference. Solutions of negatively charged gelatin caused little sedimentation of yeast cells in a solution at a pH of 4.7, which is its isoelectric point, but a very rapid rate at a pH of 8.0. Positively charged gelatin reacted similarly in relation to its isoelectric point. The rate of sedimentation of yeast cells was found to be directly proportionate to the degree of water absorption of gelatin at the pH of the solution in question. The larger the amount of unbound water, the greater the stability of the suspensoid, indicating that the individual cell may require a certain amount of unbound water to maintain suspension.

The pH of each of a series of tubes of 25% yeast in a 2% solution of negatively charged gelatin, was adjusted to represent the greatest range of pH the cells could tolerate. After standing for 1 hour the amount of cellular sedimentation in each tube was noted, and the results recorded

in graphic form. The degree of sedimentation was not uniformly progressive with changes in pH. The graphic result was a series of waves increasing in amplitude from the pH range producing the least to that producing the greatest sedimentation velocities. Erythrocytes could not be subjected to such testing because of their intolerance for pH changes.

This finding suggested the possibility that gelatin may be composed of fractions

which differ in the way they affect the sedimentation of yeast cells at a given pH. Therefore, gelatin was fractionated by the common salting-out technique. The various fractions were found to differ considerably in physical and chemical characteristics. It is not within the scope of this paper to point out in detail the differences in the various fractions of gelatin. Suffice it to say that they differ in consistency, texture, pH, isoelectric point, solubility in

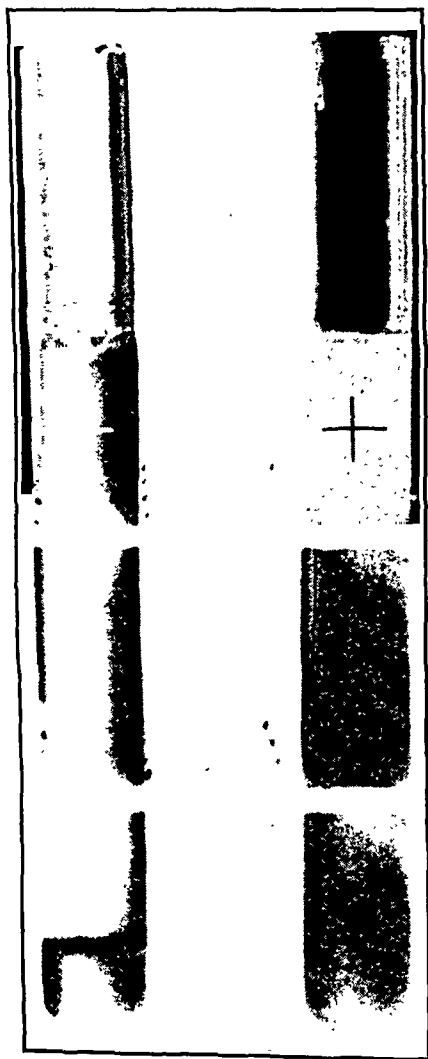


FIG. 1

FIG. 1.—Each tube in this photograph contains a 10% packed cell volume of yeast cells suspended for 30 minutes in a solution of 2% gelatin in water. The gelatin in the tube to the left carries a negative charge; that in the tube to the right bears a positive charge.

FIG. 2.—The tube to the left is of 40% packed cell volume of washed erythrocytes in a solution of 2% negatively charged gelatin in physiologic saline. The tube to the right is of the same composition except that the gelatin in this tube bears a positive charge. Photograph was taken 30 minutes after tubes were set up.

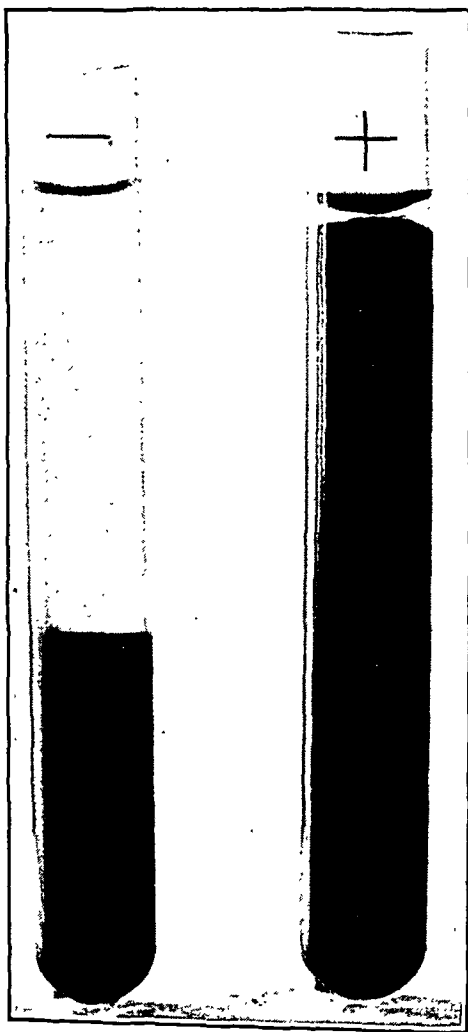


FIG. 2

water, solubility in relation to temperature, ability to produce aggregates of yeast cells or erythrocytes, and optimum pH required for clumping of these cells. The first fractions to be salted-out precipitated as a rubber-like, gummy, tenacious mass. When redissolved, these fractions were capable of producing a rapid sedimentation of yeast cells or erythrocytes. Those fractions, which were salted-out only by greater concentrations of saturated solution of ammonium sulfate, produced a precipitate which was flaky, rather than flocculant. On redissolving, they exhibited

but slight ability to cause erythrocyte, or yeast cell clumping.

(The finding that gelatin is composed of certain fractions which are able to induce erythrocytes to form aggregates, and other fractions which are relatively inert in this respect, led to the assumption that blood fibrinogen may be similarly composed. Because its plasma produces a rapid sedimentation rate, the fibrinogen of women in the last trimester of pregnancy was studied. It was found to resemble gelatin in that it, too, could be fractionated by the usual salting-out technique. It also

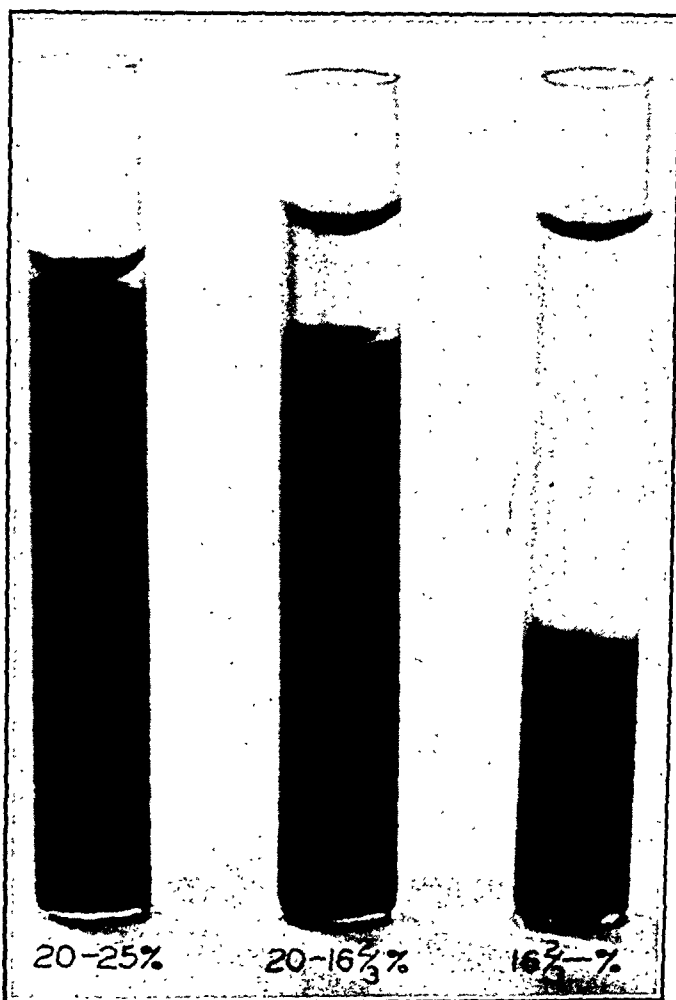


FIG. 3.—Fibrinogen from a single blood sample was fractionated into 3 parts by the common salting-out technique. Each fraction was redissolved in sufficient physiologic saline to make a 0.1% solution. Four cc. of washed erythrocytes were suspended in 6 cc. of each of the fibrinogen solutions. This photograph was taken 30 minutes after the tubes were set up. They show the influence of various fractions of fibrinogen upon the sedimentation rate. The figures below the tubes indicate the percentage of saturated solution of ammonium sulfate employed to precipitate out each of the fibrinogen fractions.

was found to be composed of fractions which were very active in causing a rapid erythrocyte sedimentation rate, and other fractions which were relatively inert in this respect (Fig. 3). Like gelatin, the fractions salted-out by the least amount of saturated solution of ammonium sulfate, caused a relatively flocculent precipitate which settled as a tenacious, rubbery mass. These fractions were found to be the ones most active in producing a rapid erythrocyte sedimentation velocity. One part of a saturated solution of ammonium sulfate to five parts of plasma, produces a solution $\frac{1}{6}$, or $16\frac{2}{3}\%$, of which is the salting-out solution. Ordinarily no great amount of blood protein is expected to be separated out of plasma by such a low concentration of this salting-out agent. However, at this concentration there is a considerable amount of blood protein separated out in those plasmas which produce a rapid erythrocyte sedimentation velocity. In our laboratory this group of proteins was called "contractinogen," because of certain physical characteristics which will be subsequently described. For convenience of expression, they will be referred to as such in this communication. The clot formed by contractinogen will be referred to as "contractin." It is not to be inferred that these are newly-discovered blood proteins, but rather that they are part of a "fibrinogen complex" which may assume qualitative changes during pregnancy and in certain disease conditions.

Contractinogen is the first of the blood proteins to be salted-out upon the addition of a saturated solution of ammonium sulfate to blood plasma; next comes the remaining portion of the fibrinogen complex and so forth. In bloods which manifest a rapid blood sedimentation rate contractinogen may constitute as much as a third of what is ordinarily considered fibrinogen. The amount is smaller in those bloods which manifest a slower blood sedimentation velocity. In a series of 90 blood samples, the amount of contractinogen was found to be directly proportion-

ate to the erythrocyte sedimentation velocity.

Contractinogen precipitates out when plasma is subjected to cooling. The amount of precipitate depends on the amount and type of contractinogen in the plasma, and the degree of cooling; this reaction is reversible. The plasma of a

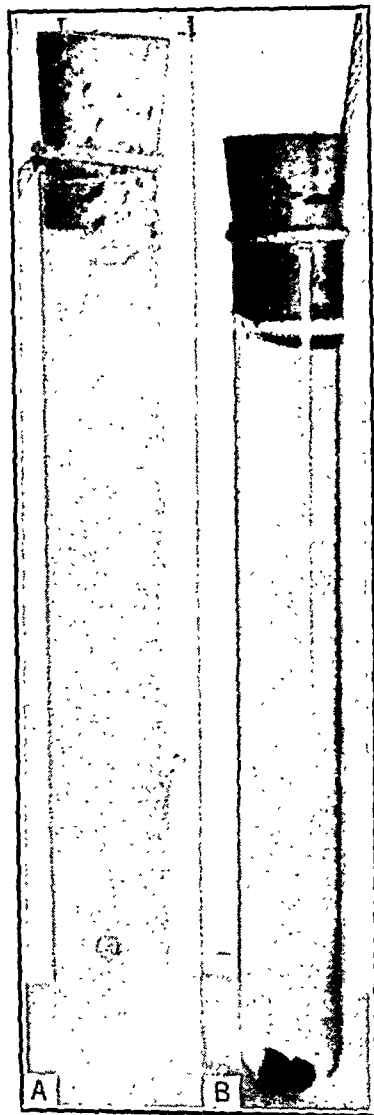


FIG. 4A.—Fibrinogen which was salted out by a 16.7% solution of saturated solution of ammonium sulfate was redissolved in water and allowed to clot. The photograph is of a test tube nearly filled by the newly formed clot which has not yet begun to retract.

FIG. 4B.—This photograph, taken 5 minutes later, is of the same clot shown in Figure 4A. In the interim the clot had been freed from the side walls of the test tube and allowed to retract down to the small, dark mass seen in the bottom of the tube.

blood with a rapid sedimentation rate will become turbid and slowly form a precipitate of contractinogen at near freezing temperatures. This insolubility could account for the influence of temperature upon the blood sedimentation rate.)

Contractinogen clots as a delicate white elastic mantle. In an aqueous solution in which the process is not impeded by blood cells, contractinogen clots more rapidly and manifests a greater ability to retract than does fibrinogen. Upon being freed from the side walls of the containing test

been allowed to stand for several hours. It also suggests a difference in the mechanism of clotting of contractinogen and fibrinogen. Experimental evidence was accidentally found which supports the opinion that various fibrinogen fractions reveal different clotting characteristics. Blood fibrinogen may be shown to clot not just once, but rather to produce a succession of clots. A successful demonstration of these phenomena requires that each successive clot be allowed to retract soon

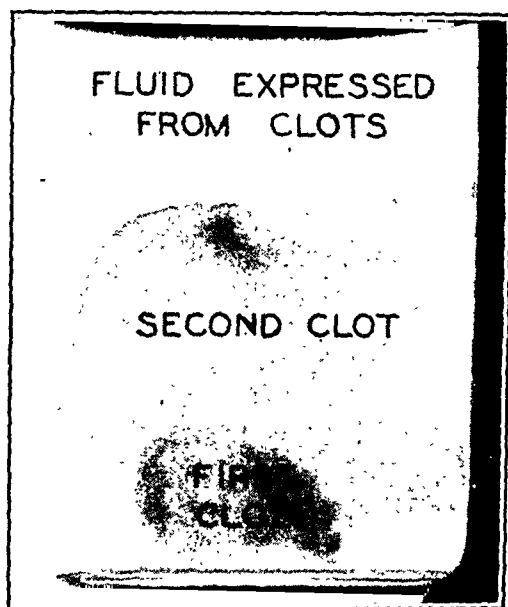


FIG. 5.—This photograph is of a clot within a clot. Each clot was formed from the same aqueous solution of fibrinogen. The first clot was separated from the side walls of the test tube and allowed to retract soon after it formed. The clear fluid expressed from the clot formed slowly into a second clot. The second clot, as did each succeeding one, revealed decreasing ability to retract.

tube, such a clot may contract down within a few minutes to a small part of its original volume (Figs. 4A and 4B). The presence of a soft, frail, mantle-like contractile clot may be demonstrable in bloods with a fast sedimentation rate which are diluted beyond their ability to form a definite fibrin clot.

{Contractinogen gradually clots out of blood plasma upon standing *in vitro*, in spite of the presence of such anticoagulants as oxalates and citrates. This may help to explain why the blood sedimentation rate becomes slower after blood has

after it is formed (Fig. 5). This work will be reported in a subsequent paper.

(Hirschboeck and Coffey, in a study of the clot retraction time in thrombophlebitis and pulmonary embolism, noted a correlation between the rapidity of clot retraction and erythrocyte sedimentation.³ They inferred from a report by Ham and Curtis² that the erythrocyte sedimentation rate was chiefly dependent on the fibrinogen level of the blood plasma. This is a view not shared by most investigators in this field. In their opinion, the increase in the amount of fibrinogen led to an increase in

the fibrin matrix of the clot. They considered this responsible for a more rapid and forceful retraction. I concur in the opinion that those bloods with a rapid erythrocyte sedimentation rate may be expected to demonstrate a rapid clot retraction time. It is my opinion that qualitative, rather than quantitative changes in the fibrinogen are the basis for this behavior. Accordingly, a rapid erythrocyte sedimentation rate or a fast clot retraction time indicates a shift of the fibrinogen complex toward those components which are most readily salted-out of plasma upon the addition of saturated solution of ammonium sulfate.

Summary and Conclusions. 1. A suspension of yeast cells in aqueous gelatin solutions may be made to mimic the erythrocyte sedimentation reaction.

2. The yeast cell sedimentation rate in gelatin solutions is dependent upon the composition and concentration of the gelatin; the electrical charge the gelatin carries; and the pH of the solution.

3. The findings, as set forth in this paper, might well be used to advantage to combat the production of rouleau forma-

tion following the therapeutic use of gelatin solutions intravenously.

4. Certain fractions of gelatin are responsible for its ability to produce a rapid sedimentation of yeast cells or erythrocytes. These fractions are the first to be salted-out upon the addition of a saturated solution of ammonium sulfate to a gelatin solution.

✓5. Fibrinogen may be divided into component parts by the common salting-out technique. These component parts display unlike physical characteristics.

✓6. The fibrinogen fractions first to be salted-out upon the addition of saturated solution of ammonium sulfate to plasma are the ones most active in producing a rapid erythrocyte sedimentation rate. These fractions precipitate out upon cooling and gradually clot out upon standing, even in the presence of anticoagulants.

✓7. Fractions of fibrinogen differ in clotting characteristics.

✓8. The fractions of fibrinogen which determine the erythrocyte sedimentation rate are probably the same ones which determine the speed and degree of clot retraction.

REFERENCES

1. FAHRAEUS, R.: *Physical Rev.*, **9**, 241, 1929.
2. HAM, T. H., and CURTIS, F. C.: *Medicine*, **17**, 4, 447, 1938.
3. HIRSCHBOECK, J. S., and COFFEY, W. L., JR.: *AM. J. MED. SCI.*, **205**, 727, 1943.
4. KARSNER, H. T., and HANZLIK, P. H.: *J. Pharm. and Exp. Ther.*, **14**, 479, 1920.
5. KENDZIORA, C. A.: Personal communication.
6. MORRISON, I. R.: *Am. J. Clin. Path.*, **11**, 578, 1941.
7. POPPER, H., VOLK, B. W., MEYER, K. A., KOZALL, D. D., and STEIGMANN, F. W.: *J. Lab. and Clin. Med.*, **30**, 352, 1945.
8. TOURTELLOTTE, D.: Personal communication.

PERSISTENT VENTRICULAR BIGEMINAL RHYTHM IN APPARENTLY NORMAL HEARTS

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PREMATURE contractions, or extrasystoles, may arise in various parts of the heart; the auricles, ventricles, or various points in the conduction system. For the most part, their occurrence is not significant, and in themselves premature beats do not indicate an abnormality in the heart. In some individuals premature beats may occur so infrequently that they are never appreciated by the individual, whereas in others they may be so frequent and persistent that they may become a source of anxiety and at times may be incapacitating by virtue of the symptoms and anxiety they cause.

The cause of premature beats of the heart is not known. Over-exertion, excitement, emotional stress and strain and fatigue are factors often related to their occurrence. Coffee, tea, alcohol, tobacco and certain drugs, for example, digitalis, may also produce premature beats. Experimentally, they may be produced by direct mechanical or chemical stimulation of the heart or by stimulation of the autonomic nervous system. They may be produced by vagal stimulation, either directly or reflexly or by stimulation of the sympathetic division of the autonomic nervous system. Allen^{1,2,3} has produced premature ventricular beats resulting in bigeminal rhythm in rabbits by mechanical stimulation of the nasal septa and has shown that the stimulus is transmitted through the sympathetic nervous system. The work of Beattie and Brow (cited by Levine⁴) indicates the presence of a center in the brain that is concerned with the formation of premature beats of the heart. It is clear then that while a number of facts are known about premature beats,

the actual mechanism of their production is unknown. There is some evidence for a structural neurogenic basis for them.

When a premature ventricular beat regularly follows each normal contraction, a bigeminal or coupled rhythm results. The commonest cause of such a rhythm is overdosage of digitalis. In other instances it may be due to organic heart disease. It may occur when premature beats arise in the auricles or the auriculoventricular node as well as when they arise in the ventricles. Rarely it may be caused by 3:2 heart block when every third auricular beat is blocked and fails to reach the ventricle. Finally, a persistent coupling of the rhythm due to premature ventricular beats may occur in apparently normal, healthy individuals in the absence of any recognizable cause. It is with these cases that this report is primarily concerned.

During the period from April 1, 1941, through October 1, 1944, a total of 3754 electrocardiograms were made in the heart station of the North Carolina Baptist Hospital in Winston-Salem, North Carolina. An electrocardiographic diagnosis of bigeminal rhythm was made in 33 instances. In 31 of these cases the bigeminal rhythm was due to premature ventricular beats; in 2 it was due to premature auricular beats. In 12 of the 33 patients the bigeminal rhythm occurred in the presence of well marked heart disease; in 13 patients it had been induced by digitalis overdosage; while in 8 patients the arrhythmia occurred in the absence of organic heart disease or of digitalis (Table 1). These patients are of particular interest, since none of the usual causes of bigeminal rhythm were present.

Four of the 8 patients in whom evidence of heart disease was lacking had very frequent, irregularly occurring premature beats, and the coupled rhythm occurred only intermittently and in short runs. These 4 patients exhibited no positive evidence of heart disease, although its absence could not be stated with certainty, since 3 of them were past 67 years of age, and all had considerable arteriosclerosis.

arthritis. There was no evidence of heart disease. The only abnormality, aside from rheumatoid arthritis, was a well marked emotional disturbance related to the skeletal deformity and incapacity caused by the arthritis. During her 6 weeks hospital stay she had bigeminal rhythm with only occasional short periods during which the rhythm was normal. We have, then, observed 2 patients who have exhibited a

TABLE 1.—THE CAUSES OF BIGEMINAL RHYTHM IN 33 CASES

Underlying cause	No. of cases
Organic heart disease	12
Digitalis	13
No demonstrable cause	8
Total	33

In 2 patients, careful examination seemed to eliminate the presence of organic heart disease. Here again the premature beats came frequently and irregularly, with only occasional short periods of bigeminal rhythm. Both patients were females in whom profound emotional factors were operating. In 1 patient the premature beats completely disappeared after the fundamental emotional disturbance was controlled. The other patient did not respond well to psychotherapy, and at the time of discharge from the hospital, premature beats were still occurring rather frequently, although the bigeminal rhythm had not recurred.

Finally, there were 2 patients who exhibited a persisting *bigeminal*, or coupled, rhythm. Neither of these patients had heart disease nor any known cause for the arrhythmia. The first was a 12 year old mentally deficient girl. She had been admitted to the hospital because of congenital nystagmus and a congenital web of the larynx. The bigeminal rhythm was due to premature ventricular beats. Physical examination revealed no other cardiac abnormalities. The electrocardiogram, except for the bigeminal rhythm, was normal. This patient was observed over 3 months, and the bigeminal rhythm was present at all times. The second patient was a 33 year old woman with rheumatoid

constant bigeminal rhythm and in whom none of the usual causes of this arrhythmia could be discovered (Table 2).

Bigeminal rhythm is not usually thought of as occurring in normal individuals. The standard textbooks of heart disease^{5,6,7} do not mention the possibility, and in the English literature we have been able to find but one reference to such an occurrence. Coogan⁴ has described persistent bigeminal rhythm of 2 years' duration in a 38 year old female. This patient had been under considerable emotional stress and strain. The bigeminal rhythm and other symptoms disappeared immediately when the cause of the emotional disturbance was removed. Coogan also cited the case of a professor who had bigeminal rhythm for 10 months while he was writing a book. The arrhythmia disappeared immediately when the strain of writing was removed. There are a number of references in the foreign literature the titles of which suggest that this condition may occur more frequently than the references in the English literature indicate. Most of the foreign references are unavailable at the present time.

The cause for the occasional occurrence of persistent bigeminal rhythm due to regularly occurring premature ventricular beats in normal persons is unknown. No attempt was made to determine the path-

ogenesis in the patients reported here. Quinidine was given to 1 patient (T.B.) without effect on the occurrence of the bigeminy. Coogan's patient had a bradycardia, and he postulated that the bigeminal rhythm was due to ventricular escape from the slow sinus rate. Atropine given to this patient speeded the heart rate and abolished the premature beat for a period of 36 hours.⁴ Most of the cases have oc-

of this arrhythmia when it occurs in persons with normal hearts.

Conclusion. 1. Bigeminal rhythm due to premature ventricular contractions may occur in the absence of heart disease and in the absence of digitalis intoxication, or other detectable cause.

2. It occurs commonly in those individuals with irregularly occurring premature ventricular beats, in which cases the

TABLE 2.—BIGEMINAL RHYTHM OCCURRING IN 8 PATIENTS IN THE ABSENCE OF DIGITALIS OR DEMONSTRABLE HEART DISEASE

A. Inconstant Bigeminy Occurring in Patients in Whom Heart Disease Could Not Be Definitely Ruled Out Because of Such Factors as Age and Arteriosclerosis				
Patient	Age	Sex	Rhythm	Associated conditions
M. B. E.	72	F	Frequent premature ventricular contractions with short, intermittent periods of bigeminy	Cerebral arteriosclerosis
M. A. B.	67	F	Same	Carcinoma of breast; benign adenoma of thyroid
F. H.	37	M	Same	Duodenal ulcer; pul. tuberculosis
J. O.	75	M	Same	Empyema; latent syphilis
B. Inconstant Bigeminy Occurring in Patients in Whom Heart Disease Could Be Definitely Ruled Out				
M. D.	48	F	Frequent premature ventricular contractions with short, intermittent periods of bigeminy	Anxiety state; menopause
T. L. T.	28	F	Same	Anxiety state; hyperven. tetany
C. Constant Bigeminy Occurring in Patients in Whom Heart Disease Could Be Definitely Ruled Out				
J. M. P.	12	F	Constant ventricular bigeminal rhythm	Mental deficiency; congenital web of larynx
T. B.	33	F	Persistent ventricular bigeminy with only rare and very short periods of normal rhythm	Anxiety state; rheumatoid arthritis

curred in females, and in most cases some emotional disturbance seemed to be an important factor. In those cases in which the bigeminal rhythm occurs only in short runs and is not persistent, it is probable that it is a chance occurrence incidental to the frequent, irregularly occurring premature beats. It seems unlikely, however, that this is true when the coupling is persistent. The necessity for a premature beat to follow regularly each normal contraction in order to produce the arrhythmia is evidence against this. Further study is necessary to determine the mechanism

coupling of the beats usually occurs only in short, intermittent periods. Less commonly it may be constant and persist for weeks or months. That the latter may occur in individuals with normal hearts is a fact not generally recognized.

3. It occurs most frequently in females and is apparently related in most instances to some emotional disorder. Usually when the emotional disturbance can be eliminated, the arrhythmia will disappear.

4. The mechanism of production of the arrhythmia in otherwise normal individuals is unknown.

REFERENCES

1. ALLEN, W. F.: Experimentally Produced Premature Systolic Arrhythmia in Rabbits, *Am. J. Physiol.*, **95**, 190, 1930.
2. ALLEN, W. F.: Experimentally Produced Premature Systolic Arrhythmia in Rabbits: Pathway of the Arrhythmia Impulse, *Am. J. Physiol.*, **96**, 243, 1931.
3. ALLEN, W. F.: Experimentally Produced Premature Systolic Arrhythmia in Rabbits: Factors That Effect Its Onset, Duration, Arrest, and Alternation, *Am. J. Physiol.*, **103**, 559, 1933.
4. COOGAN, T. J.: Analysis of an Unusual Case of Coupled Ventricular Beats, *Med. Clin. North America*, **17**, 1569, 1934.
5. LEVINE, S. A.: *Clinical Heart Disease*, Philadelphia and London, Saunders, 1937.
6. STROUD, W. D.: *Diagnosis and Treatment of Cardiovascular Disease*, Philadelphia, Davis, 1945.
7. WHITE, P. D.: *Heart Disease*, New York, Macmillan, 1937.

FUNCTIONAL PAROXYSMAL AURICULAR FIBRILLATION

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THE term uncomplicated or functional paroxysmal auricular fibrillation is used to describe the type in which no evidence of organic cardiac disease can be demonstrated. This condition occurs frequently and the literature on this subject has been well summarized by Parkinson and Campbell⁹ and also by Orgain, Wolff and White.⁸ This type of functional arrhythmia is frequently seen in Naval personnel. In a period of 3 weeks at this Naval Hospital, 5 patients were seen in consultation suffering from this variety of irregularity.

The purposes of this report are to emphasize the frequency with which the functional paroxysmal auricular fibrillation is observed in Navy personnel (and presumably in the Army) and to express our definite conviction that patients with this arrhythmia should be discharged from the Navy or retained for limited duty ashore only. This conclusion is contrary to the one implied in the many published reports^{8,9,10} which emphasize the benign nature of the irregularity. Furthermore the lessons to be learned from this study are directly applicable to civilian practice.

The 5 case histories which follow present only the salient features.

CASE 1. R. C. C., male, age 41, weight 142 pounds, height 65". This patient had been on active duty in the Chaplain Corps, USN, for 2½ years. His illness began 4½ years before admission to this hospital. Suddenly, one evening, while he was delivering his usual Sunday sermon, he had become aware of palpitation and irregular beating of his heart. He felt rather faint and had to interrupt the service. Subsequently, an electrocardiogram was taken and he was told by the physician that he had an irregular heart. He was given some pills which he thinks were quinidine. The symptoms disappeared. For the next 4 years he took very little

medication, but was frequently annoyed by spells of palpitation of variable length. These were apt to occur at any time of the day or night; they usually began suddenly and ended abruptly and lasted from several minutes to several hours. Toward the end of this period, he had short attacks almost every day, but they were never prolonged or severe enough to interfere with his usual activities.

Late in August, 1944, he was on Saipan conducting burial services for battle victims. He had been working in the hot sun, standing continuously for 3 hours, when he noticed severe palpitation and felt very dizzy. He was forced to lie down in the shade. Recovery from this episode was prompt, but his medical officer ordered him to be evacuated. He arrived at the U. S. Naval Hospital, Navy No. 10 for further treatment.

On September 17, 1944, he was seen in consultation. The past history was negative for rheumatic fever, chorea, scarlet fever and other significant illnesses. The general physical examination showed a middle aged man, of average build, in no acute distress or discomfort; there was no dyspnea. Significant findings were limited to the cardiovascular system. The heart action was grossly irregular; the ventricular rate between 90 and 150 per minute; blood pressure was about 110/80, 110/88. Cardiac size and contour were normal. No murmurs were heard. The lungs were clear; there were no signs of congestive failure. Regular sinus rhythm was readily induced by small doses of quinidine, but frequent doses were necessary to prevent reversion to fibrillation.

It was ascertained that the attacks of palpitation were more apt to occur while the patient was lying supine, and symptoms were alleviated in the prone position. Standing seemed to accentuate the symptoms of palpitation and the patient usually became dizzy if he stood for a long time or exerted himself. His habits were temperate; he usually smoked about 20 cigarettes per day and drank but 1 cup of coffee. Although he

had experimented with the possible effect of these agents, he had been unable to establish any relationship.

During periods of regular rhythm, all studies were negative. The pulse rate was usually slow, about 60 beats per minute or slightly less. Roentgen ray examination of

the chest was negative. Fluoroscopy of the heart indicated a normal size and contour with good pulsations. Basal metabolic rate was minus 5. The blood count was within normal limits. The Kahn test was negative. Sedimentation rate was normal. Psychiatric consultation resulted in a negative report.

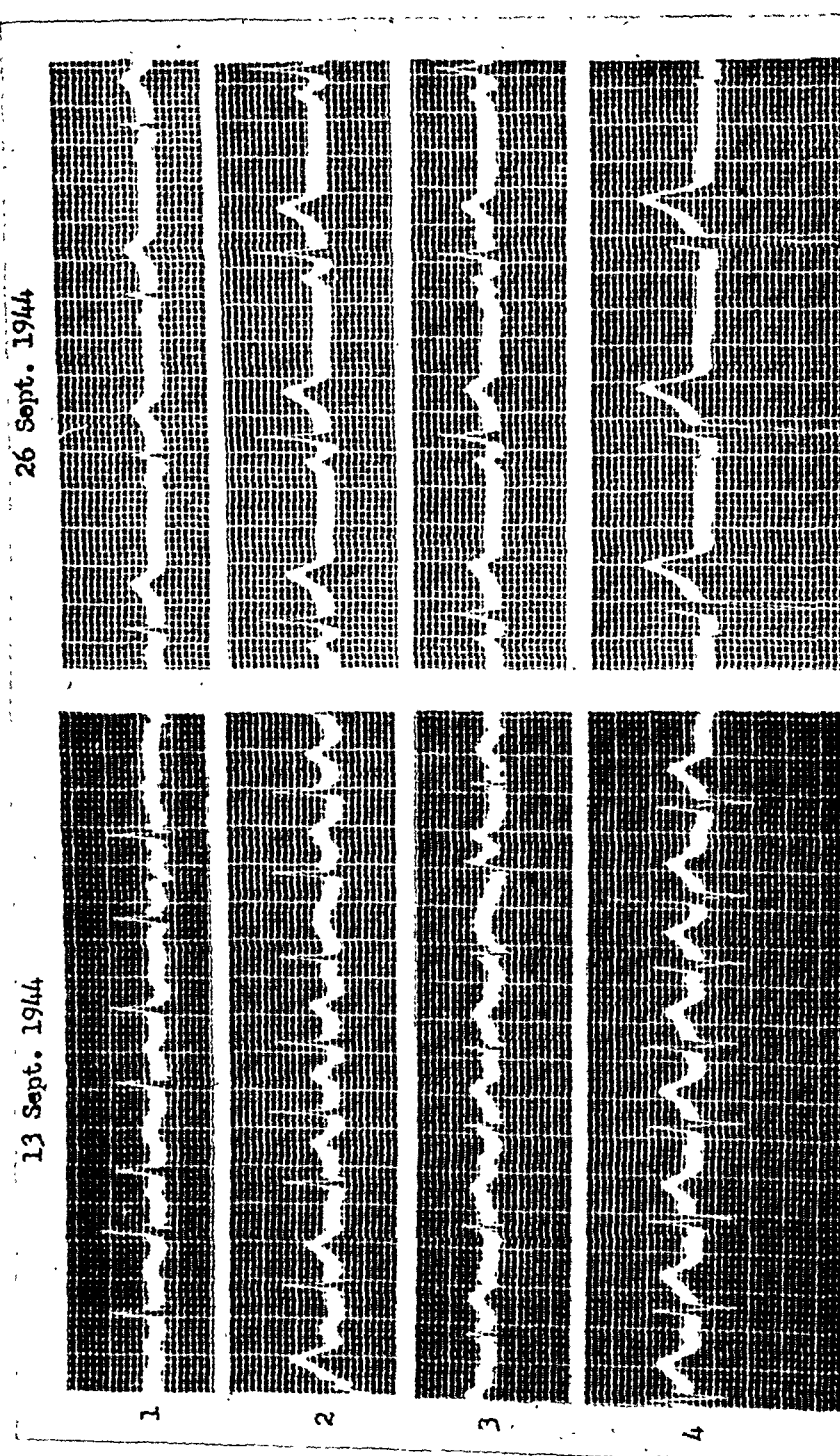


Fig. 1A.—(Case 1.) R. R. C., male, 41, C. C., USNH, Navy 10. Paroxysmal auricular fibrillation, September 13, 1944. Ventricular beat completely irregular, rate about 120 to 150 a minute, with an occasional premature ventricular systole. There is no abnormality of the QRS and T-waves; that is, no evidence of myocardial involvement. Regular sinus rhythm September 26, 1944, rate 60-64 a minute.

The control and the electrocardiograms after the "Master 2-step" exercise test were negative. In other words, there was no evidence of latent coronary insufficiency.

Without quinidine sulphate, the patient tended to have a daily reversion to auricular fibrillation. The effect of the quinidine was relatively transient and it was necessary to administer 4 or 5 tablets, each 0.2 gm. (3 gr.) per day in order to maintain a continuous regular sinus rhythm. Before evacuation the patient was able to get along with but 4 tablets a day. He was returned to limited duty in continental U. S. A., since it was concluded that his duties must not be arduous and that medical attention should always be available.

tating rest. No organic cardiovascular disease was present, and no cause for the arrhythmia was found. During the periods of regular rhythm the rate was slow and occasional premature ventricular systoles were observed. Quinidine sulphate was necessary to maintain a continuous sinus rhythm.

CASE 2. D. F. W., male, age 23, weight 170, height 5' 11". This patient was in the naval service for 2 years and had been able to perform his duties as an aviation machinist mate 2/c without any physical discomfort. The past history was negative for significant illnesses. Six weeks before admis-

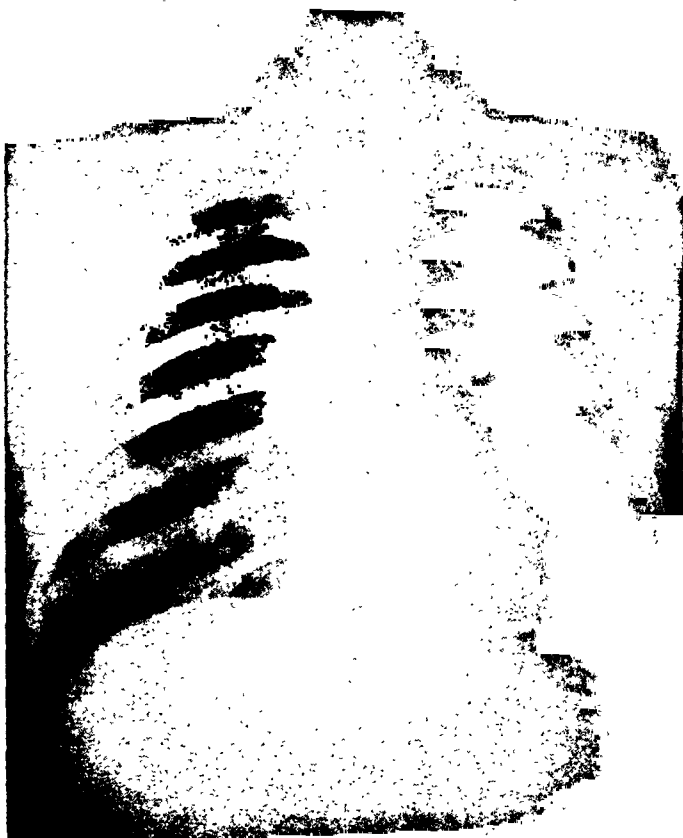


FIG. 1B.—(Case 1.) R. R. C., male, 41, C. C., USNH, Navy 10. Paroxysmal auricular fibrillation. Teleoroentgenogram discloses normal heart and lungs.

Summary. A chaplain of 41, experienced almost daily attacks of paroxysmal auricular fibrillation. During the battle on Saipan a severe episode occurred, necessi-

sion to the hospital, while engaged in his usual duties, he became suddenly aware of palpitation and irregular beating of his heart. During the following 2 weeks, these symp-

toms persisted but he continued at his work, although he avoided strenuous exertion. He sought medical advice and was turned into the sick bay. Shortly thereafter, he was transferred to this hospital. On admission, he did not appear acutely ill. The general physical examination was negative except for the following findings: the heart beat

was absolutely irregular; the apical rate was 104 per minute, the radial pulse was 84 per minute; that is, a pulse deficit of 20. The blood pressure was 98/58. There was no enlargement of the heart. No murmurs were heard and the heart tones were good. An electrocardiogram indicated the existence of auricular fibrillation but no evidence of myo-

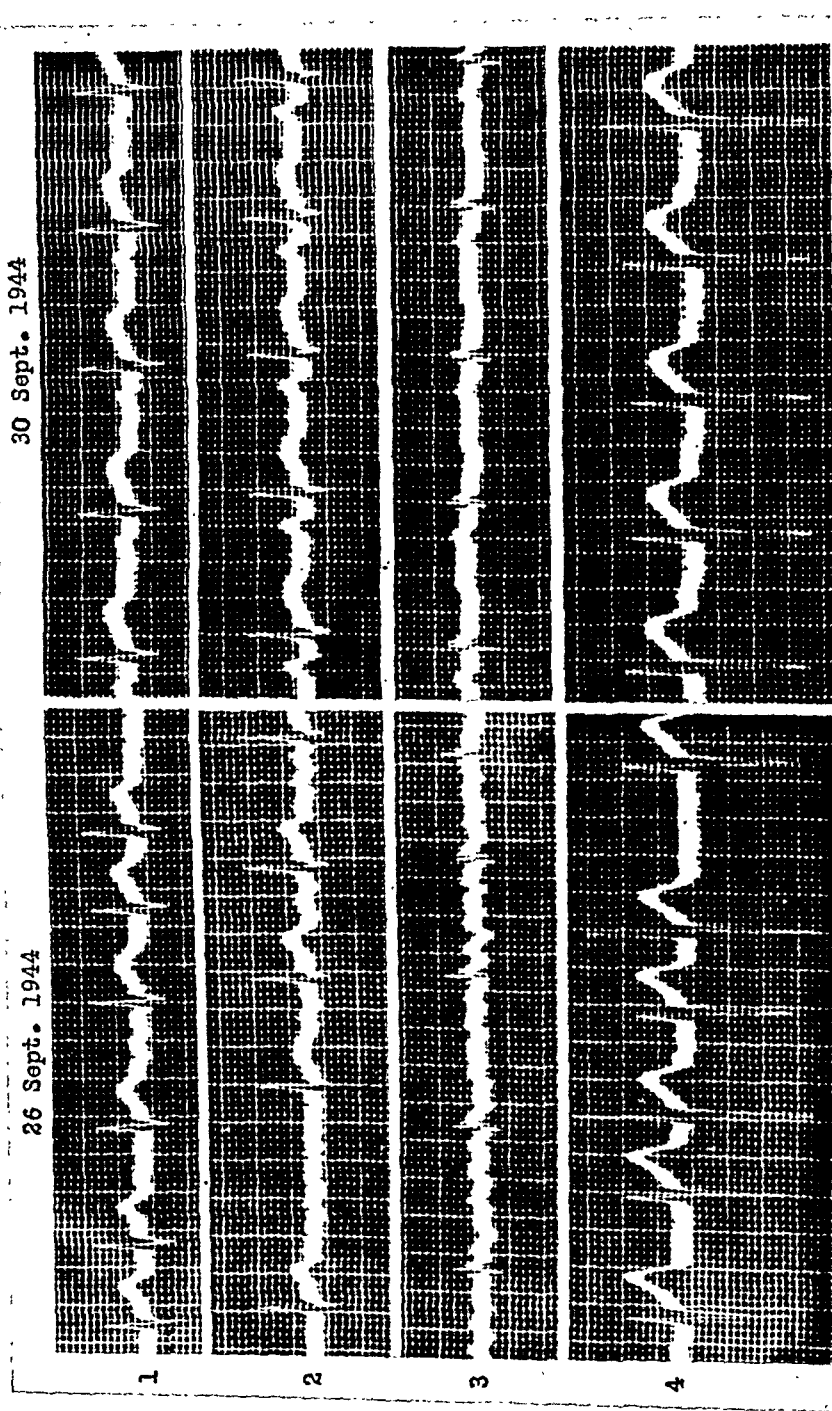


FIG. 2A.—(Case 2.) D. F. W., male, 21, AMM 2/c, USNH, Navy 10. Paroxysmal auricular fibrillation, September 26, 1944. Ventricular beats completely irregular, rate 50 to 150 a minute, with an average of about 100. There is no abnormality of the QRS and T-waves; that is, no evidence of myocardial involvement. Regular sinus rhythm September 30, 1944, heart rate 75 to 80 a minute.

cardial involvement was present; that is, there were no significant Q waves, the RS-T segments were isoelectric, and the T-waves upright. The patient was given quinidine sulphate, 0.2 gm. (3 gr.), 4 times a day. Two days later this was increased to 5 times a day, and after 2 days more it was given every 3 hours. After 48 hours of the latter dosage, the palpitation ceased abruptly and an electrocardiogram showed a normal sinus rhythm with no evidence of myocardial involvement. At this time the cardiac rate

No primary relationship could be established between the occurrence of the arrhythmia and such potential factors as body position, coffee or tea, or smoking.

Summary. A young man of 23 developed an attack of auricular fibrillation while performing his usual duties. While the arrhythmia was present he avoided strenuous exertion. Quinidine sulphate established regular sinus rhythm which was

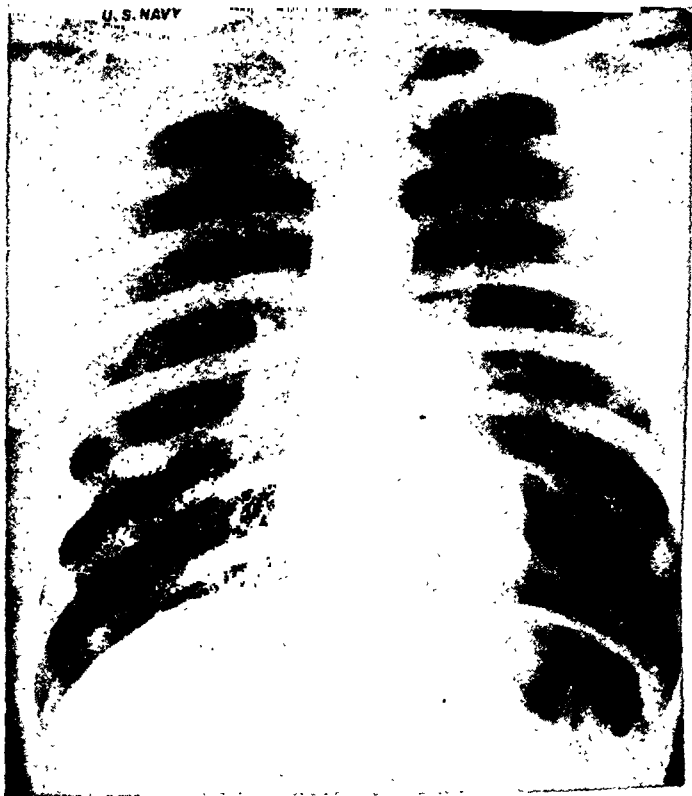


FIG. 2B.—(Case 2.) D. F. W., male, 21, AMM 2/c, USNH, Navy 10. Paroxysmal auricular fibrillation. Teleoroentgenogram September 17, 1944 discloses normal heart and lungs.

was 60 beats per minute, the blood pressure 120/72. Quinidine medication was discontinued and the regular sinus rhythm persisted. Complete studies including physical examination, electrocardiogram after "Master 2-step" exercise test, blood counts, sedimentation rate, and Kahn test were negative. The basal metabolic rate was plus 1. Fluoroscopy of the chest indicated normal cardiac size and contour, good contractions of the heart, and a normal aorta. Psychiatric consultation disclosed nothing significant.

maintained when the drug was withdrawn. A bradycardia was noted during regular sinus rhythm. No evidence of any organic cardiovascular disease was ascertained and no precipitating factor (for the attacks) was proven.

CASE 3. C. F. T., Lt. Comdr., age 48, on active duty for the past 3½ years. The patient stated that he had no serious illnesses prior to September, 1943. At this time, he

developed symptoms of acute appendicitis and at operation, a gangrenous appendix was removed. Surgical convalescence was uneventful. The day following operation, an irregular pulse was noted and subsequent investigation disclosed the presence of auricular fibrillation. He received digitalis but no additional facts were recorded in the health record. The patient gave the information that subsequent to this episode he experienced daily sensations of palpitation which were never severe enough to interfere with his duties. This palpitation would last from 15 minutes to 2 hours. On September 2, 1944, while at general quarters aboard a battleship, he had severe palpitation and collapsed. He is said to have been unconscious for about 5 minutes, and when seen by the medical officer he was clear mentally but appeared "ashen, pale and cyanotic." The pulse was completely irregular, rate about 150 per minute. The blood pressure was 50/0. On admission to this hospital, later on the same day, his only complaint was palpitation. The physical examination at the time of admission was said to have been entirely negative except for the irregular heart action. An emergency electrocardiogram was ordered but before this could be taken, the patient's rhythm had reverted to normal and the tracing was negative. It showed a regular sinus rhythm with no evidence of myocardial involvement. One week later he had another mild attack of palpitation but did not call the medical officer. On September 25, the irregularity recurred suddenly and an electrocardiogram made during the attack showed auricular fibrillation with occasional ventricular premature systoles. This attack terminated abruptly after several hours without the aid of medication. He was then placed on quinidine sulphate (0.2 gm.) twice a day as a prophylactic measure and did not have a recurrence of the fibrillation during the remainder of his stay in the hospital. When the rhythm was regular the pulse rate averaged about 56 per minute. The patient felt that while the attack was in progress he was more comfortable if he would lie flat on his back. He did not smoke, but chewed tobacco. He drank about 4 cups of coffee per day and partook moderately of beer.

Complete studies, including electrocardiograms after exercise, blood counts, sedimentation rate and Kahn tests were nega-

tive. Fluoroscopy of the heart showed normal size and contour with good pulsations and a normal aorta. BMR was plus 3. Medical discharge was recommended for this patient since it was obvious that a recurrence of the arrhythmia at a critical moment during the performance of his duties might jeopardize the safety of himself and the members of his command.

Summary. A naval officer, age 48, suffered his first bout of paroxysmal auricular fibrillation following an operation for a gangrenous appendix. Subsequently he experienced practically daily attacks. During a call for general quarters on a battleship he collapsed. While the heart was irregular, the standing position accentuated the palpitation. Quinidine was essential to maintain sinus rhythm. Premature ventricular systoles were often observed during the auricular fibrillation. During regular rhythm the heart was slow and there was no evidence of organic cardiovascular disease.

CASE 4. R. E. G. (C.M.1/c). This patient was a 39-year-old "Seabee." He had scarlet fever at the age of 2 but there was no history of rheumatic fever, chorea or diphtheria. About 8 years before he had suffered from "heart trouble" for which he was disabled about 5 months. Details of this illness were unobtainable, but apparently he had an episode similar to that for which he was admitted to this hospital. During the ensuing 8 years, he had 5 similar attacks, which lasted from 2 days to 1 month. Three weeks before admission to this hospital, he noticed the sudden onset of a sensation of "gaseous distension" and pressure on the heart followed by palpitation. He felt weak and tired since the onset of these symptoms but experienced no pain or dyspnea.

Physical examination at the time of admission revealed no abnormalities except the auricular fibrillation. The heart was not enlarged. No murmurs were heard and no accentuations were present. Apical rate was 84 and absolutely irregular; the pulse rate was 80. A pulse deficit of 4 was therefore present. Numerous moist râles were heard at the lung bases, but a Roentgen ray film of the chest taken the same day showed no

alterations of the lung fields. There was no edema of the extremities.

An electrocardiogram taken at this time indicated the existence of typical auricular fibrillation with ventricular rate varying between 60 to 80 a minute. However, there was no evidence of myocardial or valvular involvement. The QRS complexes and T-waves of the electrocardiograms were quite normal. The patient stated that his attacks seemed to follow exertion and possibly indigestion. One week later, normal sinus rhythm supervened, without the aid of medication. Examination of the heart at this time indicated normal size and contour; in fact the heart appeared small. No murmurs or significant accentuations of the heart sounds were noted. The blood pressure was 112/68. Cardiovascular studies were negative. The heart was small, with normal contour and good pulsation. The basal metabolic rate was plus 5. Blood counts, Kahn test, and sedimentation test were negative. The patient never smoked. He was evacuated to the mainland and at the time of discharge the cardiac function and rhythm were perfectly normal.

Summary. A 39 year old man developed attacks of paroxysmal auricular fibrillation, related to "gaseous distention" and exertion. He felt weak and tired. On admission he was probably in congestive heart failure for a very short time. Subsequently no evidence of organic cardiovascular disease was obtained. The ventricular rate was slow even during the arrhythmia.

CASE 5. B. H. McM., male, age 35, weight 145, height 5' 9". This patient was aware of palpitation for the past 15 years. At the inception of these attacks the palpitation was mild, but as the years passed these sensations became more pronounced and more frequent. At times he noticed only isolated and short sensations of irregular beating. At other times, the unsystematic heart behavior became established for from several minutes to several hours. The duration of the longest attack was 4 hours. The paroxysms began and ended abruptly and were apt to occur after meals either in the morning or the afternoon. The patient associated a feeling of distension with the onset of these attacks. He did not know how the

irregularity was affected by exercise because he remained very quiet while the palpitation was present. When he was not having symptoms he could exercise vigorously but he noticed that the attacks were apt to come on afterwards, while he was resting. Relief of gastric distension was obtained by taking Coca-Cola or Alka-Seltzer, which often caused the palpitation to disappear.

The past history was entirely irrelevant. He had been a refrigeration engineer before being drafted into the service 4 months previously. Since being in the service his duties consisted solely of acting as master-at-arms of the barracks. This did not entail any heavy physical or mental strain, yet the patient felt that he had been more nervous since being in the service than at any other period of his life. The patient used to be a heavy drinker but he had been very abstemious during recent years. He smoked 20 to 40 cigarettes and drank 2 to 4 cups of coffee per day.

With the exception of evidences of marked emotional instability, the physical examination was negative. When the rhythm was regular the rate was about 80 per minute; the blood pressure was 122/66. Cardiac size and contour were normal. No murmurs or abnormal sounds were present.

A typical attack occurred about 1 hour after breakfast on the day of the first examination. At this time the rhythm was totally irregular. The apical rate was about 150 beats per minute with a radial pulse deficit of about 10 to 15. The bout persisted about 15 minutes, after which the heart became regular with an occasional premature systole. The patient had been having a similar attack practically every morning of a 2-week period prior to his admission to the hospital. Electrocardiograms taken during a typical attack revealed auricular fibrillation. There was no evidence of myocardial damage. During periods when normal rhythm ensued the electrocardiograms were normal. Laboratory studies including Kahn test, urinalysis, blood count, sedimentation rate, and basal metabolism were negative.

Summary. A 35 year old refrigeration engineer with a 15-year history of frequent episodes of rapid irregular heart action. During the attacks the patient had to remain absolutely quiet. He was emotionally unstable, very nervous, smoked

20 to 40 cigarettes a day and drank 4 cups of coffee.

Comment. The auricular fibrillation was functional in origin in all our patients; no evidence of organic heart disease was found. There was no history of rheumatic fever. No hyperthyroidism was present. Physical examination, fluoroscopy, Roentgen ray films, electrocardiogram before and after exercise⁶ ("2-step"), basal metabolic rate, blood counts, urine examination and sedimentation rates all were normal. The hearts were not enlarged, there were no murmurs, no accentuations, no increased arterial tension.

Paroxysmal auricular fibrillation, functional in origin, is fairly common. It is frequently encountered in the Navy. The first 4 patients were seen in consultation within a period of but 1 week. The chief presenting symptom in our patients was "palpitation" or "pounding" of the heart. We suspect that many cases in which the diagnosis of paroxysmal auricular tachycardia is made in the history, are actually instances of paroxysmal auricular fibrillation. The patient rarely observes that his heart is irregular. Only after interrogation did 1 patient of our 5 recollect that it was irregular during the "spells" of palpitation. Paroxysmal tachycardia was the admission diagnosis of 2 of our patients. As a matter of fact, leading questions were also necessary to establish the fact that the heart rate had been rapid.

We visualize this functional type of paroxysmal auricular fibrillation very much as one does premature systoles in patients with no obvious cardiovascular disease. Ventricular premature systoles were noted in all our patients, particularly in the transition periods between the regular sinus rhythm and the irregularity or the converse. Quinidine sulphate was necessary in 2 of our patients to reestablish regular sinus rhythm and in 2 to maintain it. The same therapy is often necessary in patients who have frequent premature contractions.

The comparison between premature systoles and paroxysmal auricular fibrillation

can be carried further. Premature beats are more apt to be observed in slow hearts. Every one of our patients but the fifth had a relatively slow heart rate of about 60 beats per minute when the normal sinus rhythm was present. The cause of premature contractions is obscure and classified often as toxic, infectious and neurogenic; and so is the arrhythmia under discussion. Tobacco, coffee, liquor are common causes of both. Premature systoles alone are regarded as harmless and, if not too numerous, are no cause for rating up by life insurance companies. In the same vein, a writer¹⁰ has stated that the mortality in our type patient, that is, one with functional paroxysmal fibrillation, is no higher than in the general population.

Probably the psychogenic or nervous factor is the most potent one in the production of paroxysmal auricular fibrillation. The war has placed military personnel under unusual stress and strain and the susceptible person develops the cardiac arrhythmia through a neurogenic mechanism. Stimulation of the vagus is thought by many authors^{1,4,7,11} to be a factor in the production of paroxysmal fibrillation. Nahum and Hoff,⁷ and Iglauer, Davis and Altschule,⁴ as a result of experimental observations on animals, established a relationship between vagus stimulation and auricular fibrillation. Altschule¹ found vagal activity a factor in auricular fibrillation in rheumatic cardiac patients. Wolff¹¹ observed this functional irregularity in brothers who possessed a slow heart even after exercise.

Auricular fibrillation, paroxysmal or otherwise, due to organic heart disease, has not been observed once during many months at this overseas activity. The causes of this are usually advanced coronary, hypertensive, rheumatic, and hyperthyroid heart disease. It is reasonable to assume that personnel with such heart disease would not pass the physical examination at the time of induction into the Navy or an examination before overseas duty.

Patients with functional paroxysmal

auricular fibrillation should be discharged from the Navy or at least placed on limited duty ashore. We say this in spite of the fact that authors of numerous articles on this subject almost universally report the harmless nature of the cardiac irregularity. Willius¹⁰ states that the death rate in his patients was similar to that in the general population. We believe that his series was too small and the period of his follow-up too short. Parkinson and Campbell⁹ and Orgain, Wolff and White⁸ also emphasized the good prognosis of patients with this functional paroxysmal auricular fibrillation.

A review of the 5 cases we are reporting is enough to prove that the patients were not fit for general duty in the Navy. The Chaplain had to abandon his duties on the battlefield of Saipan. The aviation machinist's mate could not perform strenuous exertion during the arrhythmia. The Lt. Comdr. collapsed during a call to general quarters on a battleship. The 39-year-old Seabee was in congestive failure during the episode which brought him to the hospital. The last patient had to remain "very quiet" during the anomalous action of his heart. Furthermore, he had become emotionally unstable.

In civilian practice, attacks of this functional arrhythmia often prove severe enough to produce definite temporary disability. Pulse deficits are present, dizziness, faintness and occasional unconsciousness occur; often the patient is quite alarmed. Comeau² reported syncopal attacks associated with paroxysmal auricular rhythm and the establishment of auricular fibrillation. In other words, the patient is not fit for heavy work or for employment in which he is under mental strain. Thus the senior author has had the opportunity of observing this condition in engineers of "crack" trains of a large railroad company. These engineers had to be removed from their responsible jobs.

Treatment. The treatment of paroxysmal auricular fibrillation is first, removal of the cause. In Case 3, chewing tobacco

and drinking coffee may have been factors. In the last patient, the overseas duty played havoc with the patient's mental equilibrium. From the moment he learned that he was to be evacuated to the States, he became a pleasant, natural person.

Excessive exertion, mental and physical fatigue, lack of sleep, overindulgence in tobacco and coffee, gastric distension, and so forth, must be avoided. From previous experiences the victim will probably know what means are helpful in stopping an attack. Position of the body is important. Bending the trunk well forward with the head low,⁵ lying on the back and occasionally lying on the abdomen bring relief.

Complete rest is sought by the patient, for he has found that exertion prolongs the attack and aggravates its severity. Occasionally the converse is true; some physical movement like stretching the body upward is helpful. The patient should be reassured, for the cardiac irregularity may alarm him. Sedatives are often helpful.

Carotid sinus and ocular pressure should be tried, one side at a time, since reflexly this may cause cessation of the paroxysm.

Frequently the duration of the anomalous rhythm is so short that no treatment is necessary. However, to establish and maintain a regular sinus rhythm, quinidine sulphate and digitalis may be required. Given together they are synergistic and quite effective but require more care when dispensed this way. Usually quinidine alone suffices. Quinidine sulphate is first administered 3 times the first day in 0.2 gm. (3 gr.) doses. If the arrhythmia persists, the drug is given q4h, then q3h, even during the night, for quinidine is excreted in a few hours. To obviate awakening the patient during the night, a double quantity is dispensed at midnight and the 3 A.M. or 4 A.M. dose is omitted. The next step, if the cardiac irregularity is still uncontrolled, is to double the quantity of quinidine, that is, 0.4 gm. (6 gr.) instead of 0.2 gm. (3 gr.) in each dose.

If heart failure is present digitalis should be administered immediately and the patient digitalized within 24 hours. The

ventricular rate should be slowed to about 50 to 75 beats per minute. A heart beating at this rate is efficient even if irregular. Quinidine is then prescribed as previously outlined.

When the last patient was to be treated, quinidine was no longer available and so potassium acetate was used. This was administered in 1- or 2-gr. doses 3 times a day and promptly produced a regular sinus rhythm. However, when the drug was discontinued the auricles began to fibrillate again within 24 hours.

Paredrine hydrobromide³ has been recommended for paroxysmal auricular fibrillation because of its sympathetico-mimetic effect.

Summary. Paroxysmal auricular fibrillation, unassociated with organic heart disease, is not infrequent in the Navy. Emotional and mental strain, associated with the war, and excessive use of tobacco and coffee, are the probable factors in its production.

Palpitation of the heart is the chief presenting symptom. The "rapid" heart is occasionally noticed but the irregular heart action is rarely observed by the patient.

An erroneous diagnosis of paroxysmal tachycardia is frequently made by the physician. An electrocardiogram taken

during an attack will reveal a typical auricular fibrillation.

Paroxysmal auricular fibrillation is observed in patients whose normal rate is slow and who often have ventricular premature beats. The etiology of both these arrhythmias, when functional in origin, is probably neurogenic. Quinidine sulphate is the treatment for the two.

Digitalis should be administered if heart failure is present or impending. Potassium acetate may be successful when quinidine sulphate is not available. Before recourse is made to any drug, other methods for stopping an attack should be essayed. Reassurance, complete rest, certain positions of the body, carotid sinus or ocular pressure are first to be tried. The paroxysms may be prevented by avoiding excessive exertion, mental and physical fatigue, lack of sleep, excessive use of tobacco and coffee, and gastric disturbances.

Patients with this functional arrhythmia should be discharged from the Navy or retained for limited duty ashore only. They cannot carry on their regular assignments and are a danger to themselves and their comrades. Even in civilian practice there are times when this irregularity of the heart produces at least temporary disability, and those subject to it cannot perform heavy work or work associated with unusual mental strain.

REFERENCES

1. ALTSCHULE, M. D.: The Relations Between Prolonged P-R Interval and Auricular Fibrillation in Patients With Rheumatic Heart Disease, *Am. Heart J.*, **18**, 1, 1939.
2. COMEAU, W. J.: A Mechanism for Syncopal Attacks Associated With Paroxysmal Auricular Fibrillation, *New England J. Med.*, **227**, 134, 1942.
3. GRIFFITH, G. C., LT. COMDR., (MC) USNR: Use of Paredrine Hydrobromide, *U. S. Nav. Med. Bull.*, **44**, 284, 1945.
4. IGLAUER, A., DAVIS, D., and ALTSCHULE, M. D.: Auricular Fibrillation in Normal Intact Animals After the Intravenous Injection of Mecholyl, *Am. Heart J.*, **22**, 47, 1941.
5. LUTON, L. S.: Posture During Examination of Rapid Heart, *J. Am. Med. Assn.*, **123**, 693, 1943.
6. MASTER, A. M., COMDR., (MC) USNR: The Electrocardiogram and the "Two-Step" Exercise, A Test of Cardiac Function and Coronary Insufficiency, *Am. J. Med. Sci.*, **207**, 435, 1944.
7. NAHUM, L. H., and HOFF, H. E.: Auricular Fibrillation in Hyperthyroid Patients Produced by Acetyl- β -Methylcholine Chloride, With Observations on the Role of the Vagus and Some Exciting Agents in the Genesis of Auricular Fibrillation, *J. Am. Med. Assn.*, **105**, 254, 1935.
8. ORGAIN, E. S., WOLFF, L., and WHITE, P. D.: Uncomplicated Auricular Fibrillation and Auricular Flutter. Frequent Occurrence and Good Prognosis in Patients Without Other Evidence of Cardiac Disease, *Arch. Int. Med.*, **57**, 493, 1936.
9. PARKINSON, J., and CAMPBELL, M.: Paroxysmal Auricular Fibrillation. A Record of Two Hundred Patients, *Quart. J. Med.*, **24**, 67, 1930.
10. WILLIUS, L. A., and DRY, T. J.: The Prognosis of Auricular Fibrillation of Undetermined Origin, *J. Am. Med. Assn.*, **117**, 330, 1941.
11. WOLFF, L.: Familial Auricular Fibrillation, *New England J. Med.*, **229**, 396, 1943.

THE EFFECT OF SODIUM SALICYLATE ON THE SEDIMENTATION RATE OF ERYTHROCYTES IN VIVO

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THE action of sodium salicylate on the sedimentation rate of erythrocytes (Corrected Sedimentation Rate—C.S.R.) in rheumatic fever is well known⁴ and used to measure the therapeutic effectiveness of this drug.² It is also known that adequate amounts of sodium salicylate will slow down the accelerated C.S.R. *in vitro* under certain conditions.^{1,7} It is therefore of interest to establish whether this effect of salicylate, *in vivo*, is specific to rheumatic fever or whether it also occurs in conditions where the accelerated C.S.R. is not due to the rheumatic reaction.

This report deals with 3 patients who had widespread carcinomatosis with elevated sedimentation rates, in whom the administration of sodium salicylate by slowing the sedimentation rate demonstrated that this effect of the drug is not limited to rheumatic fever.

Methods. Five patients were chosen because they had elevated C.S.R.'s due to metastases of carcinomas of various organs. Intractable pain due to bone metastases was the indication for salicylate therapy. Two of the patients died during or shortly after the administration of sodium salicylate and the data obtained from them are not used here for this reason, although they are comparable to those observed in the remaining 3 patients who survived the administration of salicylate by 1 week or longer.

Patient 1 was a white female of 65, operated on in 1940 for carcinoma of the breast. During 1942–1943, pains in her legs developed due to metastases in the 5th and 6th dorsal vertebrae. In 1944, metastases were noted in the right lower lobe of the lung and the patient was admitted to the hospital because of paralysis of both legs and pain. Salicylate therapy was instituted on Oct. 24, 1944, and the experiment was discontinued on Nov. 4, 1944. The patient developed

pulmonary congestion which responded to digitalization and she died on November 18 of a left hemiplegia due to a cerebral metastasis found at autopsy.

Patient 2 was a white male of 80 years appearing about 70 years old, and admitted for intractable pain in both legs and swollen inguinal lymph nodes on the left. He had a chronic silico-tuberculosis which had been diagnosed 10 years earlier. Roentgen rays of the pelvis showed round scattered areas of decreased opacity in the left ilium. The prostate was enlarged but smooth. The diagnosis of metastatic carcinoma to bone and lymph nodes was made, the primary site remained unknown. The patient received salicylate therapy on March 19, 1945, and was followed until March 29. He remained in the hospital until May 14, when he died of an intercurrent infection. No postmortem examination could be done.

Patient 3 was a white male of 69 who had been operated on for carcinoma of the prostate in 1941. Two years later he noticed dorso-lumbar pain which became worse until his admission to the hospital on May 1, 1945, when pain due to vertebral metastases prevented use of his legs. Some rounded well-defined shadows were seen in both lung fields. This patient was given salicylate therapy from May 7 to June 11, 1945. He is at present about to undergo orchidectomy.

These patients were given sodium salicylate by mouth and by vein in the following amounts. (Sodium salicylate was given intravenously in a 1% solution of the salt contained in a 5% dextrose solution in distilled water.) Patient 1 received 10 gm. intravenously on the 1st day, 5 gm. intravenously on the 2nd day and 1.5 gm. by mouth every 4 hours, day and night on the 3rd and 4th day. Patient 2 received 4 gm. intravenously daily for 3 days and 6 gm. intravenously daily for 2 days. Patient 3 was given 4 gm. by mouth daily for 4 days, then 8 gm. by mouth for 2 days and thereafter 10 gm. by

mouth every day with, in addition, 6, 3.6 and 2.4 gm. intravenously for 3 consecutive days. The oral doses were then discontinued and 8 gm. given intravenously every day for 4 days. For 2 more days the patient received 4 gm. daily, intravenously.

The following determinations were made before therapy was started and daily thereafter: (1) C.S.R. according to Rourke-Ernstene.⁹ (2) Plasma fibrinogen levels according to Cullen and Van Slyke.³ (3) Plasma salicylate levels according to Co-

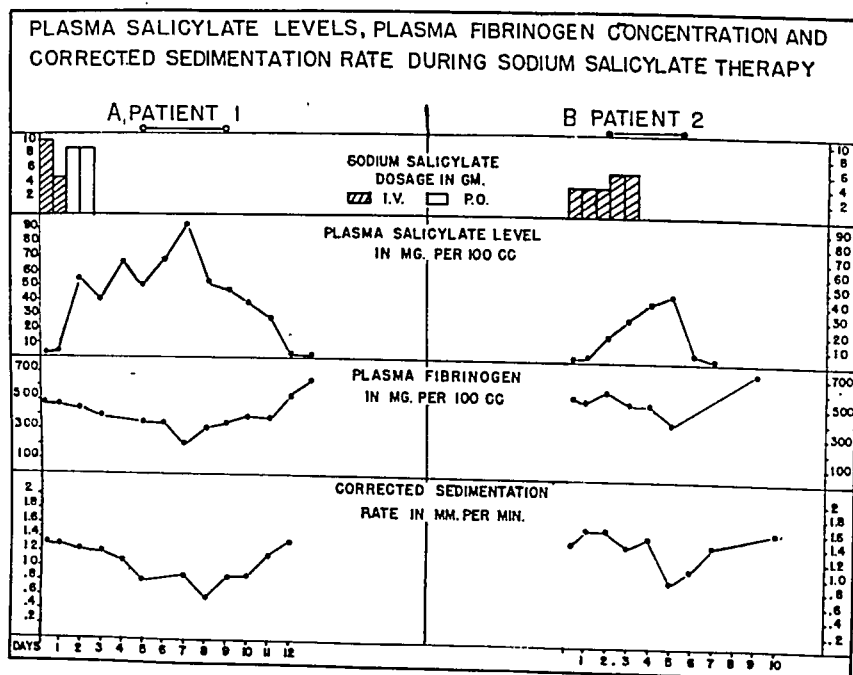


CHART 1.—Results obtained in Patients 1 and 2.

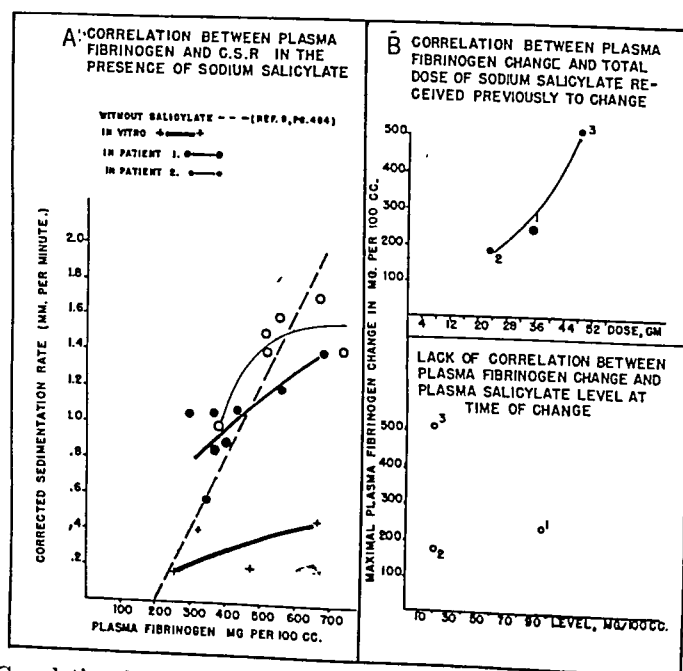


CHART 2.—A, Correlation between plasma fibrinogen and CSR. B, (upper) Correlation between plasma fibrinogen change and total dose of salicylate received previously to change. B. (lower) Lack of correlation between plasma fibrinogen change and plasma salicylate level.

burn.² (4) Prothrombin time determinations according to Quick.¹⁰

Findings regarding the prothrombin concentration will be reported later.

Results. (Chart 1, *A* and *B*.) In Patients 1 and 2 the results were comparable. After a latent period of 3 to 4 days while the plasma salicylate levels ascended, the plasma fibrinogen level and the C.S.R. did not materially change except for a slight increase of both at the beginning in Case 2. About 24 to 48 hours after the highest level of plasma salicylate concentration had been reached, the plasma fibrinogen level and the C.S.R. dropped toward normal levels.

In the third patient the plasma fibrinogen fell from 700 mg./100 ml. to 240 mg./100 ml. within the first 11 days with salicylate levels below 30 mg./100 ml. While this was comparable to the response observed in the 2 previous patients the C.S.R. did not follow the decrease of the plasma fibrinogen in the expected manner. It was then found that this patient's plasma globulin was 3.2 gm. which is enough to markedly accelerate the C.S.R. at plasma fibrinogen concentrations from normal to approximately 500 mg./100 ml. (Ham and Curtis.⁵) Later this patient developed sacral decubitus and in spite of salicylate levels as high as 60 mg./100 ml. the plasma fibrinogen level remained at 389 to 545 mg./100 ml. thereafter.

Comments. (Chart 2, *A* and *B*.) In these debilitated patients whose C.S.R. was elevated because of metastases of carcinomas, therapeutic doses of sodium salicylate clearly caused a fall of the plasma fibrinogen concentration (in 1 case following a slight increase) and a slowing of the C.S.R.

This slowing of the C.S.R. is due to the depression of the plasma fibrinogen level as sodium salicylate did not significantly modify the usual linear relation between the plasma fibrinogen concentration and

the sedimentation rate. Chart 2B shows that this relation is influenced much less than *in vitro*.

As the addition of sodium salicylate to plasma *in vitro* did not produce a fall of the fibrinogen concentration,⁷ it is unlikely that the mere presence of sodium salicylate in the blood would cause the observed plasma fibrinogen reduction. There is no actual relation between the magnitude of the change in plasma fibrinogen concentration in the patient and the plasma salicylate level at that time. However the change in plasma fibrinogen concentration is related to the total dose of salicylate received by the patient previously to the maximal change (Chart 2, *B*).

The plasma fibrinogen changes observed in these 3 patients are comparable to the findings of Irish and Jaques⁸ in dogs after administration of dicumarin. They also recall the observations of Ham and Curtis⁶ in patients with liver disease. The findings suggest that in the conditions of this experiment sodium salicylate is a hepatotoxic agent, or interferes with some other factor of fibrinogen regulation. It is questionable whether the C.S.R. is a reliable criterion for evaluation of the therapeutic effects of salicylates in rheumatic fever, as its depression by salicylate is unspecific.

Summary. 1. Therapeutic doses of sodium salicylate reduced the plasma fibrinogen concentration and the sedimentation rate of erythrocytes in patients with generalized carcinomatosis.

2. This effect can be explained by the depression of the plasma fibrinogen concentration by sodium salicylate.

3. The plasma fibrinogen is proportionate to the total dose of salicylate received by the patient and independent of the blood salicylate level.

4. The reported reduction of plasma fibrinogen following the administration of sodium salicylate is comparable to that caused by liver toxins.

REFERENCES

1. BENDIEN, W. M., NEUBERG, J., and SNAPPER, I.: Beitrag zur Theorie der Senkungsgeschwindigkeit der roten Blutkörperchen, *Biochem. Ztschr.*, **247**, 4, 307, 1932.

2. COBURN, A. F.: Salicylate Therapy in Rheumatic Fever, Bull. Johns Hopkins Hosp., **73**, 435, 1943.
3. CULLEN, G. E., and VAN SLYKE, D. D.: Quoted in Quantitative Clinical Chemistry by Peters, J. P., and Van Slyke, D. D., vol. 2, Baltimore, Williams & Wilkins, 1932.
4. ERNSTENE, A. C.: Erythrocyte Sedimentation, Plasma Fibrinogen and Leucocytosis as Indices of Rheumatic Infection, AM. J. MED. SCI., **180**, 12, 1930.
5. HAM, T. H., and CURTIS, F. C.: Sedimentation Rate of Erythrocytes, Medicine, **17**, 447, 1938.
6. HAM, T. H., and CURTIS, F. C.: Plasma Fibrinogen Response in Man, Medicine, **17**, 413, 1938.
7. HOMBURGER, F.: The Effect of Sodium Salicylate on the Sedimentation Rate of Erythrocytes *in vitro*, AM. J. MED. SCI., **210**, 168, 1945.
8. IRISH, U. D., and JAKES, L. B.: The Effect of Dicumarol Upon Plasma Fibrinogen, Am. J. Physiol., **143**, 101, 1945.
9. ROURKE, M. D., and ERNSTENE, A. C.: A Method for Correcting the Erythrocyte Sedimentation Rate for Variations in Cell Volume Percentage of Blood, Am. J. Clin. Invest., **8**, 545, 1930.
10. SOUTER, A. W., and KARK, R.: Quick's Prothrombin Test Simplified by the Use of a Stable Thromboplastin, AM. J. MED. SCI., **200**, 603, 1940.

PROGRESS OF MEDICAL SCIENCE

PREVENTIVE MEDICINE AND EPIDEMIOLOGY

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SEROLOGIC TYPES OF BACTERIA AS AN EPIDEMIOLOGIC PRINCIPLE

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EVER since the discovery of the casual relationship of microbes to disease, the methodology of the microbiologist has stressed attempts to differentiate the "pathogen" from an infinite variety of bacterial life. In the early bacteriologic literature, the constant association of a particular microorganism with a pathologic condition was sufficient for the assumption of an etiologic relationship. The widespread dissemination of microscopic life was but little appreciated. When Loeffler found his diphtheria bacillus in the throat of a man without even a suggestion of diphtheria, it almost upset his theory. Even the postulates devised by Koch did not leave room for the healthy carrier of disease producing microorganisms. And yet the school of thought which denied the significance of the newly-discovered microorganisms opposed the teachings of Pasteur and Semmelweis on the etiology of puerperal sepsis on the grounds that the same microbes could be found in persons not ill with the disease.

The past three or four decades—often referred to as the "Golden Age of Bac-

teriology" have brought an endless succession of tests and techniques, all designed to differentiate the pathogens and elucidate the meaning of its presence in the carrier as well as the disease process. The increasing knowledge of the natural history and biology of bacteria, and the concurrent development and improvement of techniques in related fields such as biochemistry and immunology have resulted in the modern serologic techniques available to the bacteriologist and epidemiologist for the classification of bacteria. The antigenic analysis of bacteria by these refined techniques has increased immeasurably our knowledge of the biology of bacteria and has provided a stability and reproducibility in systematic classification which was conspicuously lacking in earlier systems based entirely on morphologic or biochemical characteristics. However, the serologic separation of the various bacterial species into groups, types and subtypes has, on the whole, contributed remarkably little towards its original purpose—the recognition of the pathogen; or, for that matter, towards the basic

mechanics and processes involved in infection. Indeed, present-day knowledge of "virulence" in most cases is but little advanced from that of Weigert,¹¹³ who as long ago as 1875 asked whether the "something" that renders a microorganism virulent is a vital bacterial product or merely "something" attached to the microorganism.

SYSTEMATIC SEROLOGIC CLASSIFICATION. Landsteiner,⁶⁶ Wells,¹¹⁵ and Zinsser, *et al.*¹²¹ as well as several others have called attention to the extreme complexity of cellular and protoplasmic antigens as compared with isolated and purified antigens. Species specificity usually can be demonstrated for intact erythrocytes with high-titer species-specific antisera. Nuttall⁸³ showed that serologic results in general confirm zoologic classification. However, no one knows exactly what constitutes a bacterial "species." While the available evidence suggests that each so-called bacterial "species" possesses a species-specific antigen, the existence of such a fraction cannot always be demonstrated by serologic methods employing unaltered antigens. Indeed, the results of agglutination and absorption tests suggests that most bacterial "species" are not represented in the zoologic plan by a species-specific antigen, but, rather, by two or more antigenic types or sub-types. It is only by the use of special techniques that a species-specific antigen can be demonstrated among many of the bacteria.

In general, most bacterial species can be placed into one of three broad groups by serologic methods. The following is a partial list of the commoner microorganisms falling into each of these three groups:¹⁰⁴

I. SPECIES IDENTIFIED WITH A HIGH-TITER, SPECIES-SPECIFIC ANTISERUM.

1. *E. typhosus*
2. *M. tuberculosis*
3. *P. pestis*
4. *H. pertussis*
5. *Br. abortus*
6. *T. pallidum*
7. *S. aureus*
8. Certain Clostridia

II. SPECIES REPRESENTED BY A NUMBER OF DISTINCT ANTIGENIC TYPES, SOME SUB-TYPES AND PERHAPS A HETEROGENEOUS GROUP.

1. *S. hemolyticus*
2. *N. gonorrhæa*
3. *N. meningitidis*
4. *Shigella*
5. *Salmonella*
6. *Friedländer's bacilli*
7. *Pneumococci*
8. Certain Clostridia

III. SPECIES OF EXTREME ANTIGENIC HETEROGENEITY, IMMUNE SERA OF LITTLE VALUE IN SPECIES IDENTIFICATION.

1. *Escherichia coli*
2. *Pseudomonas aeruginosus*
3. *C. diphtheriæ*
4. Aerobic spore bearers
5. *S. viridans*
6. *B. proteus*
7. Certain Clostridia

Perhaps the most thoroughly studied bacterial species, with respect to serologic classification, are the pneumococci, the meningococci, the influenza group, the enteric group and the streptococci. Among these four species, well over 200 separate serologic types have been described. In the pneumococci, meningococci, clostridia and influenza group (especially the latter), serologic classification has (and still has in certain instances, regardless of drug and antibiotic therapy) a therapeutic usefulness, irrespective of whether or not the type-specific antigens are related to the ability of the microorganism to produce disease. On the other hand, there is as yet no therapeutic reason for serologic type differentiation among the enteric group or the streptococci. The pneumococci, the meningococci, the enteric group and the streptococci only will be considered in detail here, since the type classification of these microorganisms has been most extensively applied to epidemiologic studies. Of the remaining groups, two deserve mention, although type differentiation is employed almost exclusively for therapeutic reasons.

THE CLOSTRIDIA. The Clostridia associated with gas gangrene are unusual in that toxigenic type can be correlated with serologic type.¹⁰⁴ Whether or not the polysaccharide determining serologic type is a part of the toxin molecule, lending

type specificity to the various toxins of the strains in this genus is not yet known. In any case, the clinical disease induced by the various toxigenic types is essentially similar, differing only quantitatively.

Two other types of *Clostridia* are of interest in that each presents a similarity or contrast to the gas gangrene group. *Clostridium tetani* has been separated into at least six serologic types by agglutination tests. However, all agglutination types produce an antigenically identical toxin. On the other hand, *Cl. botulinum* is another exception to the general rule that different strains of the same microorganism produce the same toxin. At least five types of *Cl. botulinum* exist, each of which produces a toxin antigenically distinct from that produced by other types.

The studies of Meyer, *et al.*⁷⁶ on differences in the geographic distribution of the various toxigenic types of *Cl. botulinum* suggests an epidemiologic reason for the observation that toxigenic type causing the majority of cases of botulism varies with geographic location.

THE INFLUENZA GROUP. Although the serologic classification of *Hæmolytica influenzae* is of foremost importance in the therapy of influenzal meningitis, few epidemiologic studies have been done on the distribution of the various types. It has been observed that the carrier rate for untyped *H. influenzae* does not appear to show the seasonal fluctuations observed in the carrier rates for other microorganisms.⁸

Any one of six serologic types of *H. influenzae* occasionally produces influenzal meningitis. However, Type B is the predominant type associated with disease. Silverthorne and Paterson¹⁰⁶ have shown that carriers of *H. influenzae* Type B are rare, usually being found only in the immediate vicinity of cases, and in many instances not even under these circumstances.

THE PNEUMOCOCCI. The epidemiology as well as the clinical and pathologic aspects of pneumococcal infection have been reviewed by Heffron,⁵³ while the

varied aspects of the biology of the pneumococcus have been compiled and catalogued in an extensive work by White.¹¹⁹ The discussion of the pneumococci here is intended only to point out some of the epidemiologic similarities and contrasts between the relationship of the serologic types of pneumococci to pneumococcal infections and the serologic types of other microorganisms to the disease processes they induce.

The pneumococcus is perhaps second only to the streptococcus with respect to the multiplicity of ills it can inflict on mankind—lobar pneumonia, bronchopneumonia, sinusitis, otitis, mastoiditis, meningitis—to mention only a few. To date, well over sixty serologic types are recognized, and there seems to be no specific correlation between serologic type and clinical diagnosis, although certain types tend to predominate as the cause of some pneumococcal infections. For example, there seems to be a difference between the serologic types predominating in lobar and bronchopneumonia. Heffron⁵³ indicates that in general, Types I, II and III are the predominant causes of lobar pneumonia, and states that the distribution of types in bronchopneumonia approximates the distribution of the various types in the buccal cavities of normal persons. Heffron presents a table based on data from East Africa, Germany, Great Britain, India and the United States in which Type I appears in 6.3% of the cases of bronchopneumonia, Type II in 4.3%, Type III in 14% and the remaining types (Group IV) in 75.3% of all cases reported. The total percentage of cases accounted for by Types I and II combined (10.6%) is in sharp contrast to the total percentage of cases of lobar pneumonia (53.4%) caused by Types I and II (Table 1).

These data give only a composite picture of the world at large. There are, of course, seasonal and local variations in the predominance of the various types in pneumonia at a given time.¹¹⁹ Family and

institutional outbreaks^{95,109} have been caused by various types at different times and in different places; such outbreaks usually being due to a single serologic type.

PNEUMOCOCCUS CARRIER RATES. It has been claimed that the frequency of pneumococcus carriers increases with the advent of cold, unsettled weather.¹⁵ Such observations suggest the traditional interpretation, *viz.*, that an increased carrier rate as a result of "crowding" precedes the appearance of pneumococcus pneumonia.

Pneumococcus carriers may be transient, chronic or sporadic. In any case, the pneumococcus types predominating in lobar pneumonia are usually rare among carriers other than those convalescing from lobar pneumonia or in the immediate vicinity where cases are occurring. Gundel and Schwarz⁴⁸ for example, found that types other than Types I, II and III accounted for well over 60% of pneumococcus carriers, Type I was present in only 0.8%, Type II in 0.4% and Type III in 6.7% of the carriers studied. Rosenau, Felton and Atwater⁸⁹ isolated Type I pneumococci four times as frequently, Type III twice as frequently from persons in contact with cases of lobar pneumonia as in those with no immediate contact with cases. Curiously enough, there appeared to be little difference in the incidence of Type II among the contacts and non-contacts, while pneumococci of the remaining types were isolated from 83.5% of the contacts as compared with 69.3% of the non-contacts. On the other hand, as already mentioned, the frequency of types found in bronchopneumonia is similar to the distribution of pneumococcus types among carriers.

It would seem, then, that except under circumstances such as an institutional or family outbreak of pneumonia, a study of the carrier rates by serologic type can add little to the knowledge of the epidemiology of pneumonia. Even the presence of Types I, II and III in carriers

does not necessarily predict the occurrence of cases since there is no knowledge as yet of the factors predisposing to pneumonia on the one hand, and on the other, of why some types or certain strains of the same type gain predominance over other types which may be present in a population group. The similarity of the distribution of various types among carriers and in cases of bronchopneumonia suggests that bronchopneumonia is a chance phenomenon, perhaps dependent upon changes in the autarceology of the host rather than differences in the infecting parasites.

RELATIONSHIP OF TYPE TO DISEASE. Although the ability to produce pneumonia or other pneumococcal infections is not dependent upon serologic type *per se*, there are striking differences in the mortality rates resulting from pneumonia due to different serologic types. Heffron⁵³ cites mortality rates of 25%, 41% and 45 to 60% respectively for Types I, II and III. The data on mortality for the remaining types are scattered, but those available suggest a mortality of around 30% in untreated (serum) cases. "Virulence" is a relative term and is dependent upon a number of factors, hence there is yet no adequate explanation as to why the mortality of Type III cases should be so excessively high. Differences in "invasiveness" probably is not the entire explanation, since pneumococcemia frequently occurs in pneumonia patients and usually presents a grave prognosis regardless of serologic type.⁶ The serologic classification of the pneumococci, with the consequent studies of the capsular polysaccharides and their relationship to type-specific immunity has added little to our knowledge of the fundamental mechanics of pneumococcus infection. Despite the success of specific therapy based on serologic type, the reasons for the differences in disease producing capacity of various types, and of individual strains of the same type have not yet been explained. Whether the capsular polysaccharides are toxic in

themselves or combine with substances in the body to form toxic products, or whether the capsular polysaccharide lends antigenic specificity to a conjugated protein common to all types is not yet known. From an epidemiologic viewpoint, the ability of all types to produce disease suggests a common denominator, either host variations, or the long-sought but still elusive "pneumococcus toxin."

since so far as is known, immunization with standard typhoid vaccine protects against all bacteriophage types. Further study may reveal differences in the geographic distribution of various types in typhoid fever, probably correlating with the distribution of carriers of the various bacteriophage types.

SHIGELLA DYSENTERIÆ. The genus *Shigella* today is represented by twenty

TABLE 1.—PERCENTAGE DISTRIBUTION OF SEROLOGIC TYPES OF PNEUMOCOCCI IN LOBAR PNEUMONIA (14,869 CASES)

Location	Percentage distribution			
	Type I	Type II	Type III	Others
North America	31.5	19.2	11.8	37.5
Europe	38.7	28.3	7.0	26.0
Africa	19.1	12.2	2.2	66.5
Far East and Australia	41.0	15.4	6.6	37.0
Average	32.8	20.6	10.8	35.8

THE ENTERIC GROUP. The studies of Craige^{20,21} on the bacteriophage typing of *Eberthella typhi*, while not strictly a serologic method, deserve mention because of their epidemiologic significance. On the basis of sensitivity to various bacteriophages, ten types and several sub-types of *E. typhi* can be differentiated. The present-day epidemiology of typhoid fever being primarily a matter of carrier-contact infection, typhoid typing has increased tremendously the value of the typhoid carrier register to the epidemiologist investigating an outbreak. If the type of organism carried by the known typhoid carriers in the vicinity is known, and the cases occurring in the outbreak are typed, it is a simple matter to incriminate or exclude a carrier of responsibility.³⁸ Furthermore, single source outbreaks are usually of a single type, while multiple type outbreaks usually indicate water or sewage as the source.^{20,38} As with other microorganisms, the recognition of types has become of some use to the epidemiologist although type *per se* is not correlated with the ability to produce typhoid fever. Indeed, among the typhoid bacilli, at least, it is clearly evident that "typheness" is incidental to the ability to induce disease,

species of medical importance, which are fairly well differentiated by biochemical as well as serologic methods.¹¹ Any one of these serologic types can produce clinical dysentery in man, although there are variations in the frequency with which the various types are associated with disease from time to time in different places. Epidemiologically, bacillary dysentery, or more strictly, shigellosis, since the *Salmonella* also may incite clinical "dysentery," is largely a matter of carrier-contact infection, either direct or food-borne. Since extensive outbreaks of the disease usually originate with a food-handler, the differentiation of these microorganisms by type is of considerable use to the epidemiologist in the search for carriers incriminated in an outbreak. However, type differentiation is of no value either in the recognition of dangerous carriers among those who give no history of having had the disease or in therapy, since all types produce an essentially similar clinical syndrome. A possible exception, insofar as therapeutics is concerned, is the reported success of sulfadiazine in cases caused by *Shigella dysenteriae*.¹¹⁴

RELATION OF TYPE TO DISEASE. Although the distribution of various *Shigella*

types is known to vary over large areas, data for the United States is scanty. The studies of McGinnes, *et al.*⁷⁵ Hardy, *et al.*⁵¹ Mayfield and Gober,⁷⁴ and Wheeler¹¹⁶ seem to concur in the opinion that *Sh. paradyenteriae* (Flexner organisms) is the predominant cause of endemic dysentery in this country. On the other hand, a recent report by Nelson, *et al.*,⁸⁰ indicates that in a study done in the southeastern area of the United States, *Sh. sonnei* was isolated more frequently than all other types combined. Even in the states covered by this survey, there was a shifting of predominant type from state to state. It appears that the *Shigella* types most frequently isolated from sporadic cases were those types enjoying widest geographical distribution. There is insufficient data to determine whether these most recent findings indicate a shift in the prevalence of *Shigella* types or are the result of local conditions.

Despite our knowledge of the bacteriology of dysentery, the answer to the problem of infection by these microorganisms is still unsolved. The clinical symptoms of dysentery, on the whole very much alike, cannot be easily reconciled with the variety of types of microorganism which are so different in their biochemical and physiologic activities. For example, a *Shigella* usually associated with mild disease is not infrequently recovered from a severe outbreak, while those types (*Sh. dysenteriae* or *Sh. sonnei*), usually considered as toxic and the incitants of severe epidemic dysentery, are frequently recovered from a mild, sporadic case.

Boivan, Corre and Lehoul¹³ suggest that the reason for this seemingly paradoxical situation may be that the so-called group antigen, a carbohydrate-lipid complex common to various types of *Shigella* as well as other Gram negative microorganisms, appears to be the "enterotoxin" factor, rather than any of the as yet recognized type antigens.

THE SALMONELLA GROUP. If the existence of twenty species of *Shigella* is dif-

ficult to reconcile with the essentially similar clinical disease each can induce, then the types existing among the *Salmonella* are entirely beyond any hope of reconciliation with the clinical syndrome of Salmonellosis. At the present time, there are more than 164 strains or types of microorganisms of the *Salmonella* group which can be differentiated by the Kauffmann-White schema.¹¹ About 25% of these strains have been isolated from human infection, the remainder being of various animal or avian sources.⁹ Although the majority of *Salmonella* types are not of immediate origin, all members of the genus *Salmonella* must be considered as potential etiologic agents of sporadic or epidemic gastro-enteritis and enteric fever in man.

The widespread dissemination of the genus *Salmonella* in man and lower animals provides a variety of possible sources for accidents of environmental sanitation giving rise to an outbreak of enteric fever or Salmonellosis. One of the earliest uses to which *Salmonella* typing was put was the differentiation of the organism into either the "animal" or the "human" group, thus giving the epidemiologist an indication of where to look for the source of infection. However, Rubenstein, Feemster and Smith⁹¹ point out that by the epidemiologic and bacteriologic study of contacts of sporadic cases, institutional outbreaks, etc., they were able to demonstrate case to case spread of *Salmonella* infections due to several serologic types. These authors also point out that type studies have proven the importance of a temporary carrier state following infection with any one of several types, as well as the importance of missed or subclinical infection in the propagation of new cases. These same authors emphasize the existence of permanent *Salmonella schottmülleri* (*Sal. paratyphi* B) carriers. Indeed, a re-examination of the epidemiology of *Salmonella* infections in the light of *Salmonella* type-classification led these authors to question the thesis that the con-

stant interchange of *Salmonella* between other hosts and man rather than human to human contact is the most significant factor in the transfer of *Salmonella* infection. In other words, as with other infections, *Salmonellosis* spreads through a population by means of small groups of clinical and subclinical infections, thus considerably altering the control measures to be instituted in their control.⁹¹ Serologic type is indispensable to the epidemiologic study and control of *Salmonella* infection.

RELATIONSHIP OF TYPE TO DISEASE.

As already mentioned, about 25 % of the recognized types of *Salmonella* have been isolated from human disease. Infections due to various types of *Salmonella* are essentially similar clinically. Rubenstein, Feemster and Smith⁹¹ point out that even the time-honored distinction between *Salmonella* fever and septicemia is perhaps as unjustified as would be a distinction between typhoid fever and typhoid septicemia.

There are certain analogies between the distribution of *Salmonella* types and that of the pneumococci and streptococci in disease, in that although all strains can induce disease in man, a few serologic types predominate in a given locality. In Massachusetts, for instance, between the years 1937-43, 22 types of *Salmonella* were isolated from cases and carriers. Of 811 cases studied, 70 % were produced by four serologic types. These same four types also occurred most frequently in routine stool cultures taken for some reason other than clinical illness.³⁰ The data on the geographic distribution of *Salmonella* types is still too limited to permit generalizations as to the extent or permanence of a type-pattern, but there is some evidence suggesting variations from time to time and place to place. Seligmann, Sophra and Wassermann¹⁰³ published a comparison of the distribution of *Salmonella* types in Massachusetts and Connecticut, 1939-1942. The distribution was much alike in each state; *Sal. typhimurium* and *Sal. schottmülleri* (*Sal. paraty-*

phi B) was commonest, relatively more common in Connecticut, while on the other hand, *Sal. choleraesuis* was less common in Connecticut than in Massachusetts. *Sal. senftenberg*, appearing in an institutional epidemic in Massachusetts, was not encountered in Connecticut. The data cited by Seligmann, *et al.* suggest that the rarer types of *Salmonella* at least are often peculiar to a certain area at a given time.

From the standpoint of therapeutics, type-specific serum therapy, as with the Shigella, is unsatisfactory. There is some evidence that type differentiation may be of some value in drug therapy, since sulfanilyl-guanidine exhibits a selective action on different types of *Salmonella*.¹²

THE HEMOLYTIC STREPTOCOCCI. The hemolytic streptococcus is perhaps the most universally important of that group of microorganisms producing disease in man. There is no other bacterial species which is capable of producing in the human host the multitude of serious lesions and the variety of clinical manifestations as has been attributed to this micro-organism, ranging from inapparent infection, a transient sore throat or tonsillitis, to the acute fulminating infections in infants and young children, or the fatal toxemias and septicemias sometimes associated with puerperal fever and scarlet fever. There are few pathogens too, which can boast of the serious sequelæ of infection—such as permanent cardiac damage or acute nephritis. Its seemingly infinite importance to the economy of mankind is re-emphasized by each addition to our knowledge of its habits and biology.

The hemolytic streptococcus has occupied the attention of the medical bacteriologist in one way or another almost continuously since its discovery. During these years a tremendous volume of literature has accumulated concerning clinical manifestations, diagnostic schema, classification, etc. An excellent historic survey of the development of the classification of streptococci from the work of Schottmüller to the serologic classifications of Griffith

and Lancefield has been published recently.³¹ Perhaps the most outstanding characteristic of the early work on the classification of the streptococci was the tendency of most investigators to follow the precedent of Ogston, Fehleism, and Rosenbach by assigning species names and attributing specific pathogenic abilities to the streptococci isolated from each of the infinite manifestations of streptococcal infection. For example, the terms "*Streptococcus scarlatinæ*" and "*Streptococcus epidemicus*" appeared in the literature as the specific etiologic agents of scarlet fever and septic sore throat respectively.

The theory of species specificity among the streptococci has given rise to perhaps one of the most long-standing and heated disputes in modern bacteriology. On the other hand, the epidemiologist has long been confronted by evidence that the two are closely related. Sydenham,¹¹¹ in 1676 coined the name "scarlet fever," and referred to it as a disease in name only. As long ago as 1880 the occurrence of "sore throat" was noted in the epidemiologic study of milk-borne and contact outbreaks of scarlet fever.⁹⁹ These non-scarlatinal cases (often in siblings of patients with the classical picture of scarlet fever) were considered as "scarlatina sine eruptione," or as Trousseau referred to them, "scarlatine frust." The question of species specificity was more or less settled by Okell in 1932⁸⁴ when he demonstrated that sore throat, puerperal fever, erysipelas (streptococcal), scarlet fever and so-called surgical scarlet fever are all associated with a single hemolytic streptococcus, or possibly variants of a single type. His concise views of the unitarian concept of the pathogenesis of hemolytic streptococcal infection in man—the view that different clinical pictures were the manifestations of different equilibria between the same parasite and its hosts, did not deny the existence of antigenic types, or the preponderance of a particular type (or types) in certain kinds of infection—an analogy to the prepon-

derance of a few particular types of pneumococci in lobar pneumonia.

Griffith⁴⁷ later succeeded in establishing the existence of antigenic types among the hemolytic streptococci, thus lending bacteriologic support to the then more or less revolutionary views of Okell. Later work in this country and in England has shown that all except four of Griffith's original type strains belong to Lancefield's Group A,⁶⁵ the serologic group to which the majority of strains producing human infection belong.

Thus, the modern classification of the streptococci is based on their antigenic structure. The majority of strains can be classified into groups on the basis of a group-specific carbohydrate. Although several serologic groups contain different serologic types, the type-classification of Group A strains is perhaps the most important as well as the most complex. Group A strains are classified as to serologic type on the basis of type-specific proteins; either by Griffith's⁴⁷ slide agglutination test involving the so-called "T" antigen, or the more recent precipitation technique involving the "M" antigen.¹¹⁰ Either technique has its advantages and disadvantages; the choice of methods depending largely upon the purpose for which the results are intended. Epidemiologically, it seems that in general, one technique will yield information just as useful as the other, since the value of type classification lies primarily in the recognition of a single strain in any series of cases under study.

HETEROGENEITY OF SEROLOGIC TYPES IN STREPTOCOCCUS INFECTIONS. Concurrent with the prolonged dispute with reference to species specific etiologies for streptococcal infections, there has even persisted an undercurrent of doubt in the minds of some, as to whether or not the hemolytic streptococcus is actually related to scarlet fever. Certain discrepancies in the chain of evidence in favor of the streptococcus, and the indirectness of some of its supporting observations rather than

any validity in the claims advanced from time to time in favor of other micro-organisms^{16,17,72,73} have been responsible for the retention of the idea of a non-streptococcal etiology. As recently as 1912, Frost,³⁶ in a report describing an outbreak of septic sore throat in Baltimore stated, "Also, while the pretty constant occurrence of a rather unusual variety of streptococcus in connection with so many cases indicates most strongly that the disease was a specific streptococcus infection, there remains at least the possibility that the streptococci were of secondary importance, as in measles and scarlet fever."

The older concept of "*Strep. scarlatinae*" not only was erroneous, but tended to over-simplify the relationship of the hemolytic streptococcus to scarlet fever, as well as the relationship of other species-specific streptococci to other streptococcal infections. The application of serologic classification to epidemiologic studies of streptococcus infection has shown that species specificity does not exist among the streptococci even in the sense that it does among the meningococci; viz., the epidemiologic relationships of Type I meningococci in cerebrospinal meningitis. On the contrary, with the streptococci there appears to be no fixed relationship between serologic type *per se* and clinical diagnosis, or, for that matter, the ability to produce disease. As stated by Brown and Schaub,¹⁴ "*Strep. scarlatinae*" is not the streptococcus of scarlet fever, but is a streptococcus of scarlet fever.

The serologic heterogeneity of the streptococci producing scarlet fever as well as other streptococcal infections has been repeatedly demonstrated since Griffith⁴⁷ first published his studies on the type classification of "*Strep. pyogenes*." In view of the studies reported by the Dicks,²² Griffith's observations were not so acceptable to those who still clung to the idea of species specificity—one disease—one toxin—one microorganism. This apparent discrepancy has now been explained by

the repeated observation that the common erythrogenic toxin, the so-called "N. Y. -5" toxin is produced by most Group A streptococci regardless of serologic type. From these and the observation that serologically identical strains producing an identical toxin can be isolated from non-scarlatinal infections, has evolved the modern concept of scarlet fever, namely, that the scarlatinal rash is a symptom, not a disease. As has been pointed out by Gordon⁴¹ and others,⁹⁸ the occurrence of a scarlatinal rash is dependent upon the susceptibility of the host to erythrogenic toxin; a Dick negative subject may contract a non-scarlatinal infection from a case of scarlet fever, and transmit the infection to contacts in whom a scarlatinal rash will appear. The Dicks²² resurrected the term "*scarlatina sine eruptione*" to explain the patient infected but without a rash, since even in their inoculation experiments certain subjects became ill but did not develop a rash. However, the present day concept of scarlet fever as related to streptococcal infection in general does not permit the use of such a term.

In Table 2 it may be seen that during a given period of time in a given locality, the serologic types of hemolytic streptococci producing scarlet fever occur with about the same frequency in non-scarlatinal infections. Of the 26 original Griffith types belonging to Lancefield Group A, 22 were found to produce scarlet fever in Massachusetts during the periods of time represented in Table 2. The serologic types which do not appear in this table (Types 3, 22, 23, 30) have all produced scarlet fever at other times in different places.

DISTRIBUTION OF SEROLOGIC TYPES IN SCARLET FEVER. A summary of the various serologic types of hemolytic streptococci isolated from scarlet fever and from non-scarlatinal infections at different times in different parts of the world shows that no single type of hemolytic streptococcus is peculiar to a particular clinical diagnosis,

and that predominant types may vary from one country to another, or from year to year in the same country or community.^{33,98,118} However, two or three predominant serologic types occur as a major cause of scarlet fever in a given community (despite fluctuations in predominance).^{33,42,58,118} The occurrence of a variety of types other than those predominating in the community serves to emphasize the heterogeneous etiology of scarlet fever. Moreover, the occurrence of these same serologic types in non-scarlatinal infections emphasizes the essential unity of streptococcal infection in general.³³

logic types vary in toxin production from time to time and from place to place. The appearance and persistence of a predominant type pattern in a community suggest that locally and temporally certain types are the most successful rash producers.¹¹⁸ The serologic types of hemolytic streptococci predominant in scarlet fever might be compared in epidemiologic behavior with the pneumococcus types predominant as causes of pneumonia.

EPIDEMIOLOGIC SIGNIFICANCE. Aside from establishing the heterogeneity of the hemolytic streptococci and the essential unity of scarlet fever and other streptococcal infection (which, by the way, seems

TABLE 2.—PERCENTAGE DISTRIBUTION OF VARIOUS SEROLOGIC TYPES OF HEMOLYTIC STREPTOCOCCI IN SCARLET FEVER AS COMPARED WITH OTHER STREPTOCOCCAL INFECTIONS

Serologic type	Massachusetts, 1938-39		Massachusetts, 1942-43	
	Scarlet fever 340 cases	Other 297 cases	Scarlet fever	Other
15	44.4	30.6	0.2	
13	29.7	12.4	0.2	
11	6.8	17.8	0.3	
1	5.6	10.8	23.9	21.2
2	5.6	2.3	36.6	30.3
12	1.5	6.4	0.9	3.0
10	1.2	0.4	0.1	
25	0.8	7.1	1.5	6.0
5	0.6	..	1.2	
8	0.6	1.0	11.0	3.0
27	0.6	6.7	0.4	3.0
29	0.6	..	0.7	3.0
6	0.3	0.7	6.3	
9	0.3	0.7		
14	0.3	..	0.3	
19	0.3	..	12.1	18.2
28	0.3	2.7		
26	0.4		
17	3.6	12.1
4	0.3	
18	0.3	
24	0.1	

Fluctuations in the streptococcus type pattern of scarlet fever, with the disappearance of certain types and the appearance or reappearance of certain other types, is probably the result of the loss or acquisition of the ability of the strain to produce erythrogenic toxin. Although there is no knowledge of the circumstances which favor or inhibit the production of erythrogenic toxin by a given strain, epidemiologic observations suggest that sero-

to have been Griffith's original purpose) the separation of Group A into its component serologic types has contributed little as yet to our knowledge of the fundamental mechanics of streptococcal infection. The development of type classification led to the hope that not only would "virulence" be explained, but that the epidemiology of streptococcal infection could be more clearly elucidated by relating the carrier to the case or the case to

another case in an orderly chain of epidemiologic circumstance. However, the finding that any serologic type may produce either scarlet fever or non-scarlatinal infections, together with fluctuations in the prevalence of the various types in the same population groups with reference to time and space, not only indicates that the ability to produce disease does not depend upon serologic type, but also that serologic type is of limited value in clarifying the epidemiology of endemic disease.

Although in clearly circumscribed outbreaks, one serologic type is usually the cause of disease,²⁵ such is not the case in the endemic form of scarlet fever as it occurs in this country today. The movement of a particular serologic type is followed with difficulty among the population in even a relatively small community. Spot maps by street address of the cases occurring over a period of 2 years in a local community failed to reveal any significant special grouping of cases by serologic type.³³ In another instance, 94 cases of scarlet fever occurred in a semi-rural community with a population of less than 7000, after an absence of 2 years. Investigation revealed that seven serologic types were involved in these few cases, the various types appearing simultaneously and showing similar fluctuations in prevalence throughout the winter and early spring months.⁹⁴

The modern concept of scarlet fever (and other streptococcal infections) embraces both the case and the carrier as sources of the new case. Although serologic type has enabled us to detect the carriers and sort them out by type, the rôle of the carrier in streptococcal disease is as yet more or less undefined. As pointed out recently,⁹² the so-called "carrier surveys" have not distinguished between the healthy or "normal" carriers and the convalescent case. Since most carrier studies have been done at the time and in the place that scarlet fever was occurring, such a distinction may have a direct bearing upon the problem.

The seasonal increase in hemolytic streptococcus carrier rates has been interpreted as a precursor of an outbreak of streptococcal disease. Schwentker, Janney and Gordon⁹⁸ noted a cyclic rhythm in the gross and Group A carrier rates, the peak being reached during the late autumn and winter months, and the lowest in the summer months. As regards season, the same cyclic phenomenon has been observed in New England,³³ and can be correlated with the seasonal incidence of streptococcal disease, either in New England or the U. S. Registration Area.³³ Such similarities in the frequency distribution of two phenomena suggest a basic underlying cause common to both. Hence, it appears impossible to distinguish between cause and effect—whether or not streptococcal disease is dependent on the carrier rate or *vice versa*. Since the same types producing disease usually are found among the carriers, the evidence for either interpretation is confusing.

In the Roumanian study⁹⁸ it was observed that some factor other than the lack of toxigenic strains must be responsible for the absence of scarlet fever since there was little difference in the streptococcal flora between communities with and without scarlet fever. Incidentally, the distribution of Dick positive individuals is not the entire answer since the distribution by various age groups in communities free of scarlet fever was much the same as in other parts of the world, and in those communities when scarlet fever occurred, the distribution of positive Dick reactions was similar to the age distribution of scarlet fever.

Schwentker, Hodes, Kingsland, Chenoweth and Peck,⁹⁷ in a study of a company of naval recruits, observed that the type pattern observed in streptococcal illness was essentially the same as that found among the carriers. Where more than one type of hemolytic streptococcus was producing disease, it was found that the number of cases produced by a given type was proportional to the carrier rate for

that type. In this instance, the streptococcus carrier rate was high—69% as compared with the usual 10% in the general population. On the other hand, a sharp increase in the cases of streptococcal illness has been observed in a population group which showed no increase in the carrier rate over the level maintained prior to the appearance of cases.³² In a study by Hamburger, Hilles, *et al.*⁵⁰ it seemed that despite a changing population, the type pattern of cases of streptococcal illness admitted to an Army Station Hospital remained fairly constant over a period of 2 years, suggesting that the problem is not entirely a question of the accumulation of carriers in a population group. Hamburger⁴⁹ further observed that with as few as one or two streptococcus carriers present, cross infection may spread rapidly on open wards, while on the other hand, cross infection might not occur on other wards where the streptococcus carrier rate was as high as 50%.

Coburn¹⁸ suggests that such differences in the dissemination of a particular type at different times in different places, is the result of adaptive changes by the microorganism with relation to the changing immune state of the host under the conditions of infection. This property of adaptation may be quickly lost, but so long as it exists the microorganism possesses a high degree of "communicability." Some support is found for such a theory in the observation that the incidence of streptococcal infection is directly proportional to the carrier rate for the serologic type producing the cases. However, it has been repeatedly observed that the incidence of streptococcal infection (and streptococcal carriers) follows a definite curve related to progression of season.³³ Furthermore, the seasonal fluctuation in the streptococcus carrier rate has been shown to be due to variations in the incidence of Group A strains, the non-Group A strains maintaining a more or less constant level throughout the year.^{32,96} It seems, then, that if an increase in the

carrier rate or in "communicability" precedes the appearance of streptococcal infection (rather than *vice versa*) the non-Group A flora of the human throat should show a seasonal variation similar to that of the Group A flora, unless one is willing to apply a hypothesized seasonal difference in "transmission" or "communicability" to a particular group of strains. In any case, regardless of the nature of the mechanisms involved, it seems apparent from the accumulated evidence that the ability to "spread" or produce clinical disease is not related to serologic type.

It is not to be inferred that the carrier plays no part in the dissemination of streptococcal disease. Coburn¹⁸ described a series of cases directly attributable to convalescent carriers. Studies on scarlet fever in schoolrooms⁹³ and in households³⁵ reveals the importance of the convalescent carrier and the subclinical case in the dissemination of infection. The point is that even with the present day knowledge of serologic type at our disposal we can neither ascribe exact significance to the so-called "healthy carrier," nor can we sort out and segregate the "dangerous carrier" by the nature of the microorganism he harbors.

On the other hand, fundamental concepts of the epidemiology of streptococcal infection may be gained by the application of serologic classification to the study of the spread of infection in basic epidemiologically related units of population. Milk-borne outbreaks, for example, usually are due to a single serologic type of streptococcus, and much has been gained concerning differences in the clinical manifestations of streptococcal infection in different hosts exposed to the same strain of microorganism.^{25,107} It has been found, too, that single type outbreaks of streptococcal disease are not uncommon in schoolrooms,⁹³ institutions,⁶¹ and households,³⁵ when the application of serologic classification enables the epidemiologist to trace the spread of infection through the contacts of the primary cases. It is of value,

too, in the study of the effect of chemoprophylaxis on carriers and cases⁹² and in the control of cross infection on open wards and in institutions, especially those devoted to the case of rheumatic fever patients.^{49,61}

ANTIBACTERIAL IMMUNITY. One of the earliest attempts to immunize against streptococcal infection (scarlet fever), came soon after and followed the pattern of Jenner's work on smallpox. In a book published in 1806, Becker¹⁰ described a method then in use. Blood from the cut skin of a scarlet fever patient was rubbed into scarifications on the arm of the person to be immunized. During an epidemic of smallpox in a small Ohio village, Hudson⁵⁶ tells of seeing a man who had been exposed to smallpox and thought he had it. Hudson vaccinated the whole family, and returning next day, found that his patient had scarlet fever and not smallpox. Believing he had accidentally found a method of immunization against scarlet fever, Hudson suggested that smallpox vaccination be done early in the course of scarlet fever, and the resulting scales be used to immunize others. Hudson actually used the scabs from the arms of 2 boys in the family he first visited to immunize about 30 children, of which 23 developed mild scarlet fever. Although the discovery of erythrogenic toxin has resulted in considerable knowledge of antitoxic immunity, the sum total of knowledge concerning antibacterial streptococcus immunity and methods of inducing it are almost as vague as Hudson's primitive immunization techniques.

In general, although the erythrogenic toxin of most serologic types is antigenically similar, the immunologic response in the patient may be monovalent, suggesting a specific response to the type of infecting organism. Thus, if the patient is reinfected during convalescence with another type of toxigenic strain, he may suffer a relapse of scarlet fever.⁶⁷ On the other hand, given sufficient time, the immunity following a single attack becomes poly-

valent, resulting in more or less permanent immunity to the erythrogenic toxin. This immunity is primarily antitoxic, however, and does not necessarily protect against subsequent bacterial invasion by the same or other serologic types of streptococci.

Relatively little is known about antibacterial immunity to streptococcal infection; most of the observations and investigations in the past having been concerned with antitoxic immunity. It has been observed frequently that Dick positive individuals may harbor the identical streptococcus producing scarlet fever in other individuals at the moment without developing clinical or subclinical infection. The evidence that such immunity is of an antibacterial nature is indirect; for example, Kuttner and Krumwiede⁶¹ observed that rheumatic children usually do not contract streptococcal pharyngitis due to the same type more than once. However, its exact nature, whether it is type or group specific, and whether it is of parasitic or autarceologic origin is unknown.

The earlier attempts to demonstrate antibacterial immunity, all generally unsatisfactory, by agglutinin, precipitin, complement fixation and opsonin tests have been reviewed by the Dicks.²² More recently, the investigations of Loewenthal⁶⁸ and Lyons⁶⁹ suggest that an antiserum capable of protecting experimental animals must contain homologous type-specific antibodies. Platov, Dwan and Hoyt,⁸⁵ Kuttner and Lenert⁶² and more recently Rothbard⁹⁰ have demonstrated feeble type-specific antibacterial activity in convalescent antisera. These recent observations tend to support the opinion that the type-specific "M" protein is associated with "virulence." There is evidence that the "M" protein is at least partially responsible for the protective effects of antibacterial sera and vaccines,⁷⁰ and that the anti-"M" antibody brings about opsonization of encapsulated streptococci. These observations might be taken to indicate that the "M" substance

is responsible for streptococcal virulence, hence antibacterial immunity should be type-specific. However, it should be remembered that this material has been obtained in equally large amounts from avirulent strains⁶⁴ and, on the other hand, may not be contained in strains of unquestioned human "virulence."³² That it may be possible to stimulate protective antibodies with a substance not in itself related to "virulence" or the ability to produce disease is illustrated by the non-type specific immunity which can be obtained with the pneumococcus.¹⁰⁸

FACTORS OTHER THAN SEROLOGIC CHARACTERISTICS IN RELATION TO VIRULENCE. The accumulated evidence on the distribution of serologic types and groups in human disease lends support to the thesis that serologic characteristics are incidental to the ability of the streptococcus to produce disease; suggesting the existence of, an as yet undefined basic phenomenon or property common to most streptococci.

Kendall, Heidelberger and Dawson⁵⁹ have shown that hyaluronic acid, a polysaccharide originally described in vitreous humor, umbilical cord and synovial fluids⁷⁷ is one of the main components of the hemolytic streptococcus capsule. Seastone¹⁰² reported experiments in which it was shown that this substance was undoubtedly related to the virulence of hemolytic streptococci of human origin. Later Kass and Seastone⁵⁷ reported experiments supplying further proof of the relation of hyaluronic acid to streptococcal virulence by demonstrating that mice could be protected against fatal streptococcus infection by treatment with hyaluronidase, an enzyme which hydrolyzes hyaluronic acid. The importance of hyaluronic acid in the virulence of Group C streptococci has long been accepted as an established fact.⁶⁵ A similar rôle for the same substance in the virulence of streptococci of Group A and other serologic groups would be in agreement with the observations already reviewed that non-Group A strains as well as all serologic

types of Group A strains can produce disease. The capsular location of this substance in the cell, and the fact that autolysis of the capsule is associated with spontaneous phagocytosis in normal blood is additional evidence of its significance in the virulence of streptococci.¹⁰¹ It is not impossible that hyaluronic acid exists in the cell in close association with the "M" substance; it being non-antigenic in itself, association with the "M" substance may render it a complete antigen.

The nature of the enzyme systems, both parasitic and host, involved in streptococcus infection also are receiving attention, and may yield valuable knowledge altering the basic concept of virulence. Elliott²⁸ recently described an enzyme occurring in certain streptococcus cultures which destroys the "M" substance produced by the culture when inoculated at body temperature. This observation, together with the studies on trypsin-antitrypsin systems⁷⁸ and the effect of antitrypsin on the growth of streptococci⁷⁹ suggest that autarceologic variations in the host may be of fundamental importance in understanding the nature of the phenomena usually designated as streptococcal virulence. It must be remembered, as Dubos²⁶ thinks, that bacterial virulence is not due to a single substance or phenomenon; but, rather, to a summation of the effects of many substances and phenomena in both the parasite and host.

NON-GROUP A INFECTIONS. The data reviewed here on the heterogeneity of serologic types as the etiologic agents of various streptococcus infections suggest that the disease-producing capacity of the hemolytic streptococcus is not dependent entirely upon differences in serologic type—or even group antigens, but more likely upon some common denominator which exists irrespective of serologic characteristics. Evidence is accumulating that the ability to reproduce severe, often fatal infection in man is not limited to Group A streptococci.^{34, 87, 117} Non-Group A streptococcus infections, as compared to Group A

infections are admittedly rare, but do occur. Such infections usually are non-respiratory in origin. The ability of non-Group A strains to produce human infection is of interest, too, in that it raises further doubt on the long-disputed question of the rôle of the streptococcus toxins, erythrogenic factors, hemolysins, streptolysins and fibrinolysins in non-scarlatinal infection. With the exception of certain Group C⁵² and Group G strains,⁷¹ streptococci other than those belonging to Group A do not produce these substances, at least in measurable quantities (Table 3).

tive), but is serologically related to Group C. These data suggest interesting speculations as to the origin and evolution of serologic characteristics.

In Table 4 it will be noted that although the majority of Group A streptococci produce an erythrogenic toxin, not all strains produce a toxin homologous with the N.Y.5 strain.¹⁹ Although it is now well known that not all Group A streptococci produce an identical erythrogenic toxin,⁵⁵ there is no constant correlation between antigenic variety of toxin and serologic type. The heterologous toxin described

TABLE 3.—PRODUCTION OF TOXIC PRODUCTS BY VARIOUS SEROLOGIC GROUPS OF STREPTOCOCCI

Serologic group	Production of erythrogenic toxin	Soluble hemolysin	Fibrinolysin	Streptolysin	
				O	S
A*	+	+	+	+	+
C	+	+	+	+	?
G	+	+	+	+	?
B, D, E, F, H, K†	0	0	0	0	?

* Includes various serologic types.
† Probably should include Groups L, M and N.

TABLE 4.—PRODUCTION OF ERYTHROGENIC TOXIN BY VARIOUS SEROLOGIC GROUPS OF STREPTOCOCCI

Serologic group	Per cent toxic	Toxins neutralized by antistreptococcal horse serum (per cent of strains)			
		1	2	3	4
A*	83.7	75.7	11.0	6.2	7.1
C, G	9.4	0	12.5	0	87.5
B, D, E, F, H, K†	0	0	0	0	0

* Includes various serologic types.
† Probably should include Groups L, M and N.

The similarity between Group A and Group C and G strains is especially interesting in view of the fact that three of Griffith's original serologic types (Type 7, isolated from puerperal fever; Type 20, isolated from a carrier; and Type 21, isolated from scarlet fever) were found to belong to Group C, while a fourth (Type 16, isolated from puerperal fever) was found to belong to Group G.^{47,55} The analogy goes further in that the toxin-producing Group C strains are of the "human" type, fermenting trehalose but not sorbitol, as is characteristic of Group A strains. Furthermore, Group G is not only biochemically similar to Groups A and C (trehalose positive, sorbitol nega-

by Trask and Blake¹¹² was produced by Type 18, while many Type 18 strains produce a toxin homologous with N.Y.5. As another example, in the experience of the authors, the majority of Type 6 strains produce a toxin neutralized by N.Y.5 antiserum, while occasionally a Type 6 strain is encountered which produces an heterologous toxin. As yet, there is no knowledge of the circumstances favoring toxin production or determining the antigenic variety of toxin produced. Aside from the ability of several serologic types (and groups) to produce an erythrogenic toxin, it appears from the work of Aranow and Wood² that certain strains of hemolytic *Staphylococcus aureus* are capable of pro-

ducing a typical scarlatinal rash by the elaboration of an erythrogenic toxin which is antigenically related to that produced by the streptococcus.

MENINGOCOCCI. In spite of exhaustive bacteriologic and serologic distinctions, a question still confronts students of the epidemiology of meningitis which had already been raised and well expressed in the words of Hirsch written before the discovery of the meningococcus: "In a certain number of the epidemics that have been confined to the military . . . the earliest cases, and the majority of the cases throughout, occurred *among recruits*. It was natural to seek for an explanation of the fact in their altered mode of life, and more especially in the unwonted *bodily strain of their drill* or other duties of the service. Some . . . have gone so far as to make that factor the true and only cause of the disease. Other observers . . . have been less one-sided in the importance that they have assigned to these exactions of the service; and there can be hardly any doubt that they have had some effect in calling forth the disease. . . . It is clear that the significance to be assigned to that factor in the etiology is only that of a predisposing cause or an opportunity. It is much more reasonable, in my view, to connect the prevalence of meningitis epidemics among bodies of troops with their lodgment in more or less *crowded, badly kept, and insufficiently ventilated* tenements, or, in other words, with the same conditions that afford a peculiarly favorable soil for the development of this and many other infective diseases . . ." ⁵⁴ (in more modern terms, increased opportunity for transmission resulting from the urbanization of non-immunes as in measles).

The organism, *Neisseria intracellularis*, had been described by Marchiafava and Celli in 1884, but the significant study was that of Weichselbaum, who in 1887 described it in detail as the organism found in 6 cases of cerebrospinal fever. The substitution of actual laboratory tools and

the development of the experimental method for the older method of observation now become speculation, gave great emphasis to the rôle of the infectious agent. As with many other infectious diseases, the discovery of a microbial etiologic agent "revolutionized our entire conception of its epidemiology" by displacing "the then dominant and paralyzing" theories of predisposition by the "more hopeful infective theory." As has not infrequently been the case in the pursuit of medical knowledge, the trend in research took the direction of the newer techniques—not necessarily that of the truth. The central idea in epidemiology became the infectious agent and its mode of spread, but the sporadic distribution of cases even in epidemics and especially the finding of meningococci in the nasopharynx of normal people as well as in cases, soon pushed the bacteriologic study of the disease beyond the mere question of exposure to the infectious agent. With the new techniques available, the explanation came to be sought in some variation or difference in the infective agent.

Differences in strains of meningococci were first recognized in the course of the preparation of therapeutic antimeningococcus serum. Several or many strains of the organism were employed for the inoculation of animals on the supposition that biologic variations in strains would be covered. It was the observation that strains of the organism isolated from the nasopharynx of healthy persons frequently were not agglutinated by sera prepared with strains from cases which led to attempts at classification into serologic types, first with a view to a better therapeutic serum and later from the point of view of a better understanding of epidemiologic relationships. That the earlier classifications represented only an imperfect separation of distinct types of the organism, and that they had little to do with pathogenicity is indicated by cross reactions between strains of different types, by a great lack of agreement be-

tween the classifications set up by different workers, and by the fact that all types could be found both in the clinical disease and in the healthy carrier.

It has been through a long process of careful selection of strains rather than the introduction of any new principle, that the present day classification of serologic types of meningococci has evolved. That this classification has meaning is shown by the fact that clinical meningitis is now associated in the vast majority of cases with a single serologic type, and that the incidence of the disease closely parallels the prevalence of this type of organism rather than that of the other three types which are distinguished. This does not mean, however, that the different serologic types are wholly unrelated in the epidemiologic sense, for when there is a change in type composition, an increase in the frequency of one type is accompanied by a corresponding decrease in the frequency of one or more of the other types. The relative increase in frequency of one type, for example, the increase in frequency of Type I meningococci which correlates with increase in the incidence of meningitis, does not appear to represent the "introduction of a new strain," but, rather, a differentiation of other types, more especially Type x into Type I; a change which occurs for reasons which are not known.

At about the time typing of meningococci reached the point of refinement which made it a differential procedure of any degree of precision, the advent of the newer chemotherapeutic agents went far to make typing no longer necessary, at least from the point of view of the purpose for which it was originally undertaken (the production of therapeutic serum). It has, nonetheless, turned out to be the only instance of serologic typing which constitutes a method of any epidemiologic importance in differentiating organisms that produce disease from those that do not. The present day understanding of the relationship between the prevalence of a single type meningococcus and meningitis

not only throws into the discard some of the sweeping and laborious measures which had earlier been advocated as a *sine qua non* for the control of meningitis, particularly in the mobilization of armies; but revolutionizes some of the basic conceptions of the epidemiology of the disease.

The question whether meningitis is determined by "predisposing factors" or by "contagion"—raised even before the discovery of the meningococcus, gave way with the discovery of the meningococcus to studies centered entirely on the organism. Now the relationships between meningococcus carriage, in the light of serologic classification and the incidence of meningitis, reopens the same question in a somewhat modified form: *to what extent* is the incidence of meningitis determined by the dissemination of the organism, and *to what extent* is the disease determined by predisposing factors in the small portion of those who harbor a particular type of the organism? In other words, the strictly microbic point of view of a straight contest between host and infectious agent, begins to yield to the conception of a state of remarkable equilibrium between the host and parasite in which the disease occurs only exceptionally when this equilibrium is thrown out of balance by factors which, although not yet clearly understood, do not necessarily reside entirely in the parasite.

Soon after the agglutination test was introduced for the identification of meningococci, it was noticed that different strains possessed varying degrees of agglutinability. Kutscher in 1906 who employed the absorption test, observed that there was a marked difference between strains, but he was unable to classify them by this method.⁶⁰ In 1909 Elser and Huntoon found that 40% of meningococci, which they termed pseudomeningococci, were inagglutinable by a monovalent serum.³⁰ They further divided the pseudomeningococci by absorption into two sub-groups. In the same year, Dopter noticed the presence in nasopharyngeal mucus of cocci

resembling the meningococcus in morphology, cultural and fermentation reactions, but differing from it in their complete absence of agglutination with a meningococcal serum; these organisms he termed parameningococci.²³ Arkwright, also in 1909, noticed not only that by agglutination and absorption the organisms could be roughly divided into groups, but that, serologically, the sporadic strains tended to deviate more from the type to which most strains conformed than did the epidemic strains.³ In 1914 Dopter and Pauron divided the parameningococci into 3 types,²⁴ and Ellis (1915) found that strains fell into 2 types, I and II, of which Type II was probably identical with Dopter's parameningococcus.²⁵ Arkwright (1915) was able to classify 30 out of 35 strains into 2 main groups, Types I and II,⁴ of which Type II, like Ellis' corresponded to Dopter's parameningococcus; 3 strains were difficult to classify, and 2 were intermediate between the 2 types. Gordon and Murray (1915) found that strains from cerebrospinal fluid of epidemic cases fell sharply into 4 groups, which they called Groups I, II, III, and IV;⁴⁵ none showed any relation to Dopter's parameningococcus. In 1917, Nicolle, Debains and Jouan classified the meningococci into 4 types, called A, B, C, and D.⁸¹

Gordon's I and III strains corresponded to N., D. and J.'s Type A.

Gordon's II and IV strains corresponded to N., D. and J.'s Type B.

Dopter's meningococcus corresponded to N., D. and J.'s Type A.

Dopter's parameningococcus α corresponded to N., D. and J.'s Type B.

Dopter's parameningococcus β corresponded to N., D. and J.'s Type B or C.

Dopter's parameningococcus γ corresponded to N., D. and J.'s Type D.

F. Griffith (1917) found that meningococci could be divided into 2 main groups, I and II;⁴⁶ Group I corresponded roughly with Gordon and Murray's Groups I and III, and Group II with Gordon and Murray's Groups II and IV.

Wollstein observed that between the so-called normal and parameningococci

there were a number of intermediate varieties.¹²⁰ According to Amoss, the studies of the meningococcus stimulated by the appearance of epidemic meningitis in the armies of all the belligerent powers in World War I brought meningococcus typing into a period of great activity. The general point of view of the time was represented by the classifications of Gordon and of Nicolle and their associates. Briefly stated they distinguished two main types of meningococci designated either Types I and II, or A and B. Gordon also recognized Subtypes III and IV, one affiliating with Type II and the other with Type I, and Nicolle likewise distinguished two such types, C and D, which showed similar affiliations.

As Amoss says, "The serological subdivision of the meningococcus into varieties or types has undoubtedly marked a forward step in our knowledge of the causation and specific treatment of epidemic meningitis. It may, however, perhaps be regarded as of questionable value to set up too many minor varieties or types."¹¹

In Gordon's original investigation, 32 strains of meningococci were found to be resolved into 4 different groups. "As a rule, the results of simple agglutination were confirmed by the absorption test." There were "close affinities between members of Types 1 and 3, and 2 and 4, but absorption tests proved that these were due to minor or co-agglutinins, and that the major agglutinin of each of the four types was univalent and specific." Gram-negative cocci from the nasopharynx of nine contacts and one doubtful case of cerebrospinal fever were "submitted to investigation with the four univalent agglutinating sera that had been proved to include all of the serological types of meningococcus occurring in the cerebrospinal fluid of the thirty-two cases." All of these were "indistinguishable from the meningococcus in morphological, cultural, and fermentative characters." Six were found to be "serologically identical with

the meningococcus, five being specimens of Type 2, and one of Type 1." The remaining 4 could not be identified serologically with any of the 4 types of meningococcus. Two specimens were injected into rabbits and an agglutinating serum prepared against each of them. "The specific agglutinin of each of the pharyngococci, while readily removed by the homologous coccus, was unaffected by any of the four types of meningococcus obtained from the cerebrospinal fluid of the cases." Later specimens of meningococcus from the cerebrospinal fluid of cases were tested with the four univalent sera. "By the end of 1915 over sixty specimens of meningococcus had been examined with all four agglutinating sera, and found to be identical with one or the other of the four serological types."⁴³

It hardly seems surprising that Gordon's classification based on the study of such a small number of cultures should have turned out upon further study to represent a far from complete separation of types of meningococci.

The combined force of the "new" type classifications, and the pressing needs of the military situation brought about the quick elaboration of a formula to explain the epidemic occurrence of the disease, and to meet the pressure for preventive measures. It was perhaps in part its plausibility and in part its preciseness which caused it to be so widely adopted. Observations made even in the course of these very studies which under ordinary circumstances would have raised doubt, passed seemingly unnoticed. It is furthermore curious that even though serologic typing so largely gave impetus to the epidemiologic studies concerning carrier rates, the epidemiologic deductions did not take into consideration at all the various serologic types. They were based rather on overall carrier rate.

The World War I concept had it that previous to an outbreak of meningitis, "carriers of the meningococcus increased steadily," from a "normal" carrier rate

of from 2 to 4% to 20 or 30%, and that soon after it had passed the "danger point" of 20%, cases would begin to appear. A search of a very large literature of the time does not reveal any facts, or theory, for that matter, upon which a 20% "danger point" was based. There are statements concerning individual situations which, even if not of any particular significance from a statistical point of view, were so vivid that they were too readily incorporated in texts on meningitis. "The carrier-rate, which was 19.25 per cent . . . reached what is usually considered the danger point of twenty per cent (see War Office Memorandum on Cerebrospinal Fever, p. 2), just six days before the first case occurred."³⁹ Again, the carrier rate "which had been kept beautifully low during November (5 per cent. on November 29) now commenced to rise in ominous fashion; on December 6 it was nearly 17 per cent., on the 21st 19 per cent., just under the 20 per cent. danger line as laid down in the War Office memorandum." The idea was not in the least impeded by such lines as ". . . sporadic cases may admittedly arise with any carrier rate . . ."⁴⁰ and that 22% of civilians examined in an outpatient infirmary, "although they had no relation to cerebrospinal fever" harbored in their nasopharynx organisms indistinguishable from the meningococci,¹⁰⁰ a result confirming previous studies which showed that "meningococci are to be found in a considerable percentage of persons in whom no relation to cases of cerebrospinal meningitis is discoverable."

Having fixed a cause of epidemics with such a high degree of precision as the "warning rise" and "20% danger point," it was natural to hurry on to an explanation for these "sure storm signals of imminent danger." Investigating the cause of this "warning rise" in the carrier rate, Glover (1920) was led to suspect a relationship between it and overcrowding in the sleeping huts. These huts were "at the best poorly ventilated" (Eagleton,

1919-20), and during the stress of war "the mobilization standard had been overstepped," so that beds, instead of being separated, were practically touching each other. Glover (1920) noticed that the carriers in a given hut tended to be aggregated together. This pointed strongly to the direct transmission of the meningococcus from one man to another sleeping in the next bed. He tried the effect of spacing out the beds in the hope that the infection would be diminished. The results obtained "seemed to be in accordance with expectation." The effect of the distance between the beds was not confined to the carrier rate. At Caterham depot, "where there was severe overcrowding," an outbreak of cerebrospinal fever had occurred during each winter of the War, but subsequently to the adoption of the spacing-out policy in 1917-18, "not a single case occurred." It is sometimes difficult to determine whether in these studies, a high carrier rate was actually associated with overcrowding or was in itself interpreted as evidence of overcrowding. A sharp rise in the non-contact carrier rate "is as sure a storm signal of imminent danger of an outbreak as it is a sign of overcrowding or of dangerously deficient ventilation."⁴⁰ (The latter was sometimes invoked in instances of otherwise unsatisfactory evidence of "overcrowding.")

The far-reaching implications regarding the relation between overcrowding and the carrier rate; and that between the carrier rate and the disease; as well as the importance of detecting the "warning rise," were the cause of the wide acceptance of the whole doctrine, but there has been a noteworthy absence of confirmation of the main theses. In the Detroit epidemic of 1928-29, Norton and Gordon (1930) found no correlation between the degree of overcrowding in the home and the contact carrier rate.⁸² During the outbreak of 1931 at Aldershot, Armstrong and his colleagues (1931), from a study of the position of carriers in dormitory barrack rooms, were unable to obtain any

evidence that infection occurred mainly at night.⁵ The carriers were scattered quite irregularly without any particular relation to the position of the beds. Other nasopharyngeal surveys of the civilian population, like that of Rake (1934),⁸⁶ have shown us that the carrier rate in institutions may be as high as 20% and over, without any outbreak of cerebrospinal fever occurring. Perhaps the most striking figures, however, are afforded by Dudley and Brennan (1934). Working at the Chatham naval hospital, they found that between January, 1932, and March, 1933, there were 11 cases of cerebrospinal meningitis with a carrier rate of about 13%. During the period, March, 1933, to May, 1934, the carrier rate was 54%, yet not a single case of meningitis occurred. During the same period at the Royal Naval Hospital, Portsmouth, there were 6 cases of meningitis with a carrier rate of only 5%. Analysis of the distribution of carriers at Chatham showed no constant relationship between the density of the population and the carrier rate. The senior ratings with the most spacious sleeping accommodation had as high a carrier rate—60%—as the recruits with the worst sleeping quarters.²⁷

That all was not well with the World War I concept of meningitis and its prevention—that "when the carrier rate rises, it is direct evidence . . . of overcrowding; when that is remedied, the carrier rate automatically falls"⁴⁴—is further supported by reports that "measures employed to prevent meningitis . . . cannot be considered as altogether successful. In spite of the great care exercised in the isolation of cases, wholesale examinations made to detect and eliminate carriers of meningococci, and the various other methods employed to limit the spread of the disease, the incidence of meningitis in troops was much greater than in the civilian population."¹⁰⁵ Thus, after the extensive researches of the World War I period, the status of serologic typing of meningococci, insofar as it provided any

epidemiologic explanation of the occurrence of the disease, or indicated methods of control, was much the same as that of the other groups of organisms considered in this paper. But as already stated, subsequent refinements of typing, notably the work of Branham, Rake, and Kirkbride have resulted in a method which does differentiate the "pathogen."

It was this advance, together with the advent of the newer chemotherapeutic agents with the possibility of their prophylactic use, which called for further studies of meningococcus carriage, when the World War II period again coincided with one of the periodic waves of meningitis prevalence (but not necessarily causally related).

The results of these studies, not yet available for complete review, will show it is believed, that the meningococcus carrier rate (all types) is the backlog upon which the carrier rate of the "pathogen" (Type I) smoulders. Within the relatively uniform overall carrier rate, the prevalence of Type I carriage rises and falls periodically, probably as a result of changes in type in the ordinarily less highly differentiated organism in the course of its dissemination, the cause of which is yet unknown. There are indications that periods of *relatively* high Type I carriage correspond to periods of increased prevalence of meningitis, and that the occurrence of the disease in the very small proportion of those who come to harbor Type I meningococci—larger in recruits than in seasoned troops or the civilian population—may be determined "by the unwonted bodily strain of their drill or other duties of the service."⁵⁴

Summary. Serologic techniques, perhaps the most valuable tools of the modern systematic bacteriologist, have made immeasurable contributions to the present-day knowledge of bacteria. As reviewed here, the application of type differences to the study of infectious disease also has increased certain phases of our knowledge concerning the bacteriology, epidemiology

and therapeutics of infection. Type differentiation was of utmost importance, for example, before the advent of the sulfa drugs and antibiotics in the treatment of *Clostridium* infections, pneumococcus pneumonia, meningococcal meningitis and influenzal meningitis. Type differentiation, even in these days of penicillin and sulfa therapy and prophylaxis is still essential to the successful treatment of *Clostridium* intoxications, influenzal meningitis and in some cases of pneumococcal or meningococcal infection. The enteric fevers and the streptococcal infections are exceptions in that as yet serologic type seems to have no bearing on therapy, although in the case of enteric infection, type differentiation may be of some value in the selection of an appropriate sulfa compound for therapy.

From an epidemiologic viewpoint, serologic type differentiation is of some value in delineating the spread of a single strain under certain circumstances; for example, single source, institutional or family outbreaks of disease, and in the control of cross-infection on hospital wards. However, the idea that type differentiation would explain the epidemiology of infectious disease in general, or clarify the etiology of certain diseases in the sense of a single species for a single disease, has met with disappointment. With the exception of meningococcal meningitis, there is no instance of any degree of correlation between a single serologic type and a single disease process. Neither has the relationship of the carrier rate to clinical disease been established in any, other than meningococcal meningitis. The general similarity between the types of streptococci and pneumococci in normal carriers of these microorganisms and in the diseases they induce has contributed little to an understanding of the relationship between the case and the normal carrier, or in distinguishing between cause and effect with regard to case and carrier. The enteric group is perhaps slightly different in that by common agreement, all carriers

are considered as being potentially dangerous since all *Salmonella*, *Eberthella* and *Shigella* are potential pathogens. Even among the enteric group, however, serologic type affords no criterion for altering this concept by the selection and isolation or treatment of dangerous carriers.

Most disappointing of all, knowledge of serologic types has given us little insight into the basic mechanics of bacterial infection. Again, with the possible exception of the meningococcus, it is apparent that the ability of the respective microorganisms to produce scarlet fever, pneumonia, gas gangrene or enteric fever is entirely independent of type characteristics, unless one is willing to accept the thesis that in the *Salmonella* group, for example, there exists 164 separate type antigens each endowed with the same ability to incite disease in man.

Perhaps one of the fundamental faults in present-day bacteriology is our lack of a concept as to what constitutes a bacterial species. In an age of specialization, the bacteriologist is perhaps all too willing to assign the microorganisms to a specialized category, thereby overlooking for the moment the broader biologic phenomena common to a group of bacteria which actually may be of more fundamental importance than the criteria upon which a special category is selected. For example, where amongst the ponderous literature on the pneumococci, can be found any extensive studies on the observation that non-type-specific immunity can be produced against the pneumococcus, or on the host factors or host changes predisposing to lobar or bronchopneumonia?

As Brown¹⁴ recently pointed out, "Every biologist assumes that species are relatively stable; they are the result of evolution which he has no reason to believe has been suspended, but which proceeds so slowly or so intermittently that it need not deter the giving of useful names to the species which he observes. Names are labels used for convenience in description and, if possible, to indicate genetic rela-

tionship." Should the concept of species be based on serologic or biochemical type; or should the broader view—the streptococci as a species, for example—be taken in an attempt to explain pathogenicity or "virulence," meanwhile retaining the biochemical and serologic types as convenient "labels?" In attempting to define "virulence" it should be remembered that the term is relative, in all probability, as Dubos²⁶ pointed out, depending upon a number of variables, not a single isolated substance or characteristic, but, rather, upon the entire spectrum of biologic behavior, both parasitic and host. The epidemiologic observations on the diversity of serologic types associated with infection which have been reviewed here, suggest that "typeness" *per se* is perhaps only one of the many variables which determine the ability of the microorganism to produce disease. It is indeed remarkable that the vast amount of knowledge resulting from study of serologic type has contributed so little to the knowledge of the basic processes involved in infection, or for that matter, recovery. Even in a disease as thoroughly studied as lobar pneumonia, the rôle of type-specific immune response in recovery from infection is still open to question.⁸⁸

The frequent statement that evolution in science is paced by evolution in its methodology is so far from true in respect to serologic types of bacteria and the causation of disease that the question might well be raised whether the right methodology has yet been found. As Gallup had written in 1815 (long before the discovery of bacteria), "If instead of scrutinizing old shoes, rags, etc., to find imported fomites, and accusing foreigners of transporting epidemic disease, the zealous enquirers after truth had exerted their talents to discriminate and render innocuous the local causes of disease, the science of physic would have become less reproachful to its cultivators."³⁷ Perhaps not until equal attention has been directed to "typing" of autarceologic susceptibility

shall we understand those imbalances—in a broader sense, a remarkable host-which we call disease—in what may be, parasite equilibrium.

REFERENCES

- (1.) Amoss, H. L., and Marsh, P.: *J. Exp. Med.*, 28, 779, 1918. (2.) Aranow, H., Jr., and Wood, W. B., Jr.: *J. Am. Med. Assn.*, 119, 1491, 1942. (3.) Arkwright, J. A.: (Br.) *J. Hyg.*, 9, 104, 1909. (4.) Arkwright, J. A.: *Brit. Med. J.*, 2, 885, 1915. (5.) Armstrong, C., et al.: *J. Roy. Army Med. Corps.*, 57, 321, 1931. (6.) Avery, O. T., Chickering, H. T., Cole, R., and Dochez, A. R.: *Acute Lobar Pneumonia. Prevention and Serum Treatment.* New York, Rockefeller Inst. for Med. Res., Monograph No. 7, 1917. (7.) Aycock, W. L.: Unpublished paper read before the American Epidemiological Society, "A Two Year Study of Meningococcus Carriers and the Relation to Meningitis," March 24, 1944, Washington, D. C. (8.) Aycock, W. L., Lutman, G. E., and Foley, G. E.: *AM. J. MED. SCI.*, 209, 395, 1945. (9.) Barnes, L. A.: *U. S. Nav. Med. Bull.*, 41, 1184, 1943. (10.) Becker, G. W.: *Das Scharlachfieber*, Pirna, 1806. (11.) Bergey, D. H., Breed, R. S., Murray, E. G. D., and Hitchens, A. P.: *Bergey's Manual of Determinative Bacteriology*, 5th ed., Baltimore, Williams & Wilkins Co., 1939. (12.) Bornstein, S., and Strauss, L.: *Proc. Soc. Exp. Biol. and Med.*, 47, 112, 1941. (13.) Boivan, A., Corre, L., and Lehoul, Y.: *Revue d'Immunologie*, 7, 97, 1942. (14.) Brown, J. H., and Schaub, I. G.: *AM. J. MED. SCI.*, 208, 385, 1944. (15.) Brown, M. H., and Anderson, E.: *J. Prev. Med.*, 6, 407, 1932. (16.) Caronia, G., and Sindoni, M. B.: *Pediatrica*, 31, 745, 1923. (17.) Class, W. J.: *Chicago Med. Rec.*, 16, 373, 1899. (18.) Coburn, A. F.: *U. S. Nav. Med. Bull.*, 42, 325, 1944. (19.) Coffey, J. M.: *J. Immunol.*, 35, 121, 1938. (20.) Craige, J.: *Canad. Pub. Health J.*, 33, 41, 1942. (21.) Craige, J., and Brandon, K. F.: *Canad. Pub. Health J.*, 27, 165, 1936. (22.) Dick, G. F., and Dick, G. H.: *Scarlet Fever*, Chicago, Ill., The Yearbook Publishers, Inc., 1938. (23.) Dopter, C.: *Compt. rend. Soc. de biol.*, 67, 74, 1909; "L'Infection Méningococcique," Paris, 1921. (24.) Dopter, C., and Pauron: *Compt. rend. Soc. de biol.*, 77, 231, 292, 1914. (25.) Dublin, T. D., Rogers, E. F. H., Perkins, J. E., and Graves, F. W.: *Am. J. Pub. Health*, 33, 157, 1943. (26.) Dubos, R. J.: *The Bacterial Cell*, Harvard University Press, Cambridge, 1945. (27.) Dudley, S. F., and Brennan, J. R.: (Br.) *J. Hyg.*, 34, 525, 1934. (28.) Elliott, S. D.: *J. Exp. Med.*, 81, 573, 1945. (29.) Ellis, A. W. M.: *Brit. Med. J.*, 2, 880, 1915. (30.) Elser, W. J., and Huntoon, F. M.: *J. Med. Res.*, 20, 371, 1909. (31.) Ernst, J.: *The Epidemiological Significance of Grouping and Typing the Hemolytic Streptococci*, E. Munksgaard, Copenhagen, 1942. (32.) Foley, G. E.: Unpublished data. (33.) Foley, G. E., Aycock, W. L., and Cox, R. D.: *New England J. Med.*, 233, 761, 1945. (34.) Foley, G. E., and Wheeler, S. M.: *Am. J. Dis. Child.*, 70, 93, 1945. (35.) Foley, G. E., Wheeler, S. M., and Aycock, W. L.: *Am. J. Pub. Health*, 34, 1083, 1944. (36.) Frost, W. H.: *Pub. Health Rep.*, 27, 1889, 1912. (37.) Gallup, Joseph A.: *Sketches of Epidemic Disease in Vermont*, Boston, T. B. Wait & Sons, 1815. (38.) Gauthier, J., and Foley, A. R.: *Canad. Pub. Health J.*, 34, 543, 1943. (39.) Glover, J. A.: *J. Roy. Army Med. Corps*, 30, 23, 1918. (40.) Glover, J. A.: *Med. Res. Counc. Spec. Rep.*, London, Series 50, 133, 1920. (41.) Gordon, J. E.: *New England J. Med.*, 221, 1024, 1939. (42.) Gordon, J. E., Wesselhoft, C., and Smith, E. C.: Unpublished data. (43.) Gordon, M. H.: *J. Roy. Army Med. Corps*, 30, 1, 1918. (44.) Gordon, M. H., et al.: *Studies in the Bacteriology, Preventive Control and Specific Treatment of Cerebrospinal Fever Among the Military Forces, 1915-1919*, Med. Res. Counc., London, 200, 1920. (45.) Gordon, M. H., and Murray, E. G.: *J. Roy. Army Med. Corps*, 25, 411, 1915. (46.) Griffith, F.: *Rep. Loc. Govt. Bd. Pub. Health*, New Series, No. 111, 52, 1917. (47.) Griffith, F. F.: (Br.) *J. Hyg.*, 34, 542, 1934. (48.) Gundel, M., and Schwarz, F. K. T.: *Ztschr. f. Hyg. u. Infektionskr.*, 113, 498, 1932. (49.) Hamburger, M.: *J. Infect. Dis.*, 75, 58, 1944. (50.) Hamburger, M., Hilles, C. H., Hamburger, V. G., Johnson, M. A., and Wallin, J. G.: *J. Am. Med. Assn.*, 124, 564, 1944. (51.) Hardy, A. V., Watt, J., Kolodny, M. H., and DeCapito, T.: *Am. J. Pub. Health*, 30, 53, 1940. (52.) Hare, R.: *Lancet*, 1, 109, 1940. (53.) Heffron, R.: *Pneumonia with Special Reference to Pneumococcus Pneumonia*, New York, The Commonwealth Fund, 1939. (54.) Hirsch, A.: *Handbook of Geographical and Historical Pathology*, 2d ed., London, New Sydenham Soc., vol. 111, 1886. (55.) Hooker, S. B., and Follensby, E. M.: *J. Immunol.*, 27, 177, 1934. (56.) Hudson, S.: *Ohio Med. and Surg. J.*, 15, 189, 1862. (57.) Kass, E. H., and Seastone, C. V.: *J. Exp. Med.*, 79, 319, 1944. (58.) Keefer, C. S., Rantz, L. A., Shuman, H. H., and Rammelkamp, C. H.: *Arch. Int. Med.*, 69, 952, 1942. (59.) Kendall, F. E., Heidelberger, M., and Dawson, M. H.: *J. Biol. Chem.*, 118, 61, 1937. (60.) Kutscher, K.: *Deutsch. med. Wchnschr.*, 22, 1071, 1906. (61.) Kuttner, A. G., and Krumwiede, E.: *J. Clin. Invest.*, 23, 139, 1944. (62.) Kuttner, A. G., and Lenert, T. F.: *J. Clin. Invest.*, 23, 151, 1944. (63.) Lancefield, R. C.: *J. Exp. Med.*, 57, 571, 1933. (64.) Lancefield, R. C.: *J. Exp. Med.*, 71, 521, 1940. (65.) Lancefield, R. C.: *Harvey Lectures*, Series 36, 251, 1940-41. (66.) Landsteiner, K.: *The Specificity of Serological Reactions*, Springfield, Ill., Charles C Thomas, 1936. (67.) Lichtenstein, A.: *Acta Paediatr.*, 12, 95, 1931. (68.) Loewenthal, H.: *Brit. J. Exp. Pathol.*, 15, 298, 1934. (69.) Lyons, C.: *J. Am. Med. Assn.*, 105, 1972, 1935. (70.) Lyons, C., and Ward, H. K.: *J. Exp. Med.*, 61, 531, 1935. (71.) MacDonald, I.: *Med. J. Australia*, 2, 471, 1939. (72.) Mallory, F. B.: *J. Med. Res.*, 36, 483, 1903-04. (73.) Mallory, F. B., and Medlar, E. M.: *J. Med. Res.*, 35, 209, 1903. (74.) Mayfield, C. R., and Gober, M.: *Am. J. Pub. Health*, 31, 363, 1941. (75.) McGinnes, G. F., McLean, A. L., Spindle, F.

and Maxcy, K. F.: *Am. J. Hyg.*, 24, 553, 1936. (76.) Meyer, K. F., et al.: *J. Infect. Dis.*, 31, 501, 541, 610, 623, 650, 1922. (77.) Meyer, K., and Palmer, J. W.: *J. Biol. Chem.*, 114, 689, 1936. (78.) Mirsky, I. A.: *Science*, 100, 198, 1944. (79.) Mirsky, I. A., and Foley, G. E.: *Proc. Soc. Exp. Biol. and Med.*, 59, 34, 1945.

(80.) Nelson, C. T., Borg, A. F., Spizizen, J., and Barnes, M. J.: *Am. J. Pub. Health*, 36, 51, 1945. (81.) Nicolle, N., Debains, E., and Jouan, C.: *Ann. Inst. Pasteur*, 32, 150, 1918. (82.) Norton, J. F., and Gordon, J. E.: *J. Prev. Med.*, 4, 207, 1930. (83.) Nuttall, G. H. F.: *Blood Immunity and Blood Relationship*, Cambridge, Oxford Univ. Press, 1904.

(84.) Okell, C. C.: *Milroy Lectures*, 1932. Review by W. W. G. Topley, *Bull. Hyg.*, 7, 529, 1932.

(85.) Platov, E. S., Dwan, P. F., and Hoyt, R. E.: *J. Am. Med. Assn.*, 116, 11, 1941.

(86.) Rake, G.: *J. Exp. Med.*, 59, 553, 1934. (87.) Rantz, L. A., and Kirby, W. M. M.: *Arch. Int. Med.*, 71, 516, 1943. (88.) Robertson, O. H.: *J. Am. Med. Assn.*, 111, 1432, 1938. (89.) Rosenau, M. J., Felton, L. D., and Atwater, R. M.: *Am. J. Hyg.*, 6, 463, 1926. (90.) Rothbard, S.: *J. Exp. Med.*, 82, 93, 1945. (91.) Rubenstein, A. D., Feemster, R. F., and Smith, H. M.: *Am. J. Pub. Health*, 34, 841, 1944. (92.) Rubenstein, A. D., and Foley, G. E.: *New England J. Med.*, 233, 315, 1945. (93.) Rubenstein, A. D., and Foley, G. E.: *Am. J. Pub. Health*, 35, 905, 1945. (94.) Rubenstein, A. D., and Foley, G. E.: To be published.

(95.) Schroder, M. C., and Cooper, G.: *J. Infect. Dis.*, 46, 384, 1930. (96.) Schwentker, F. F.: *Am. J. Hyg.*, 38, 207, 1943. (97.) Schwentker, F. F., Hodes, H. L., Kingsland, L. C., Chenoweth, B. M., Jr., and Peck, J. L., Jr.: *Am. J. Pub. Health*, 33, 1455, 1943. (98.) Schwentker, F. F., Janney, J. H., and Gordon, J. E.: *Am. J. Hyg.*, 38, 27, 1943. (99.) Scott, H. H.: *Some Notable Epidemics*, London, E. Arnold & Co., 1934. (100.) Scott, W. M.: (*Br.*) *J. Hyg.*, 17, 191, 1918. (101.) Seastone, C. V.: *J. Bact.*, 28, 481, 1934. (102.) Seastone, C. V.: *J. Exp. Med.*, 77, 21, 1943. (103.) Seligmann, E., Sopha, I., and Wassermann, M.: *Am. J. Hyg.*, 38, 226, 1943. (104.) Sherwood, N. P.: *Immunology*, 2d ed., St. Louis, C. V. Mosby Co., 1941. (105.) Siler, J. F.: *The Med. Dept. of the U. S. Army in the World War*, Vol. IX, Washington, 1928, U. S. Govt. Printing Office. (106.) Silverthorne, N., and Paterson, M.: *Canad. Pub. Health J.*, 43, 178, 1943. (107.) Stebbins, E. L., Ingraham, H. S., and Reed, E. A.: *Am. J. Pub. Health*, 27, 1259, 1937. (108.) Street, J. A.: *J. Immunol.*, 43, 53, 1942. (109.) Ström, A.: *J. Infect. Dis.*, 50, 430, 1932. (110.) Swift, H. T., Wilson, A. T., and Lancefield, R. C.: *J. Exp. Med.*, 78, 127, 1943. (111.) Sydenham, T.: *Opera Omnia*, Edited by G. A. Greenhill, London, Sydenham Society, 1844.

(112.) Trask, J. D., and Blake, F. G.: *J. Am. Med. Assn.*, 101, 753, 1933.

(113.) Weigert, C.: *Ueber pockenähnliche Gebilde in parenchymatösen Organen und deren Beziehung Bacteriencolonien*, Breslau, 1875. (114.) Weil, A. J.: *J. Immunol.*, 46, 13, 1943. (115.) Wells, H. G.: *The Chemical Aspects of Immunity*, 2d ed., New York, The Chemical Catalog Co., 1929. (116.) Wheeler, K. M.: *Connecticut State Med. J.*, 8, 419, 1944. (117.) Wheeler, S. M., and Foley, G. E.: *J. Bact.*, 46, 391, 1943. (118.) Wheeler, S. M., and Foley, G. E.: *New England J. Med.*, 231, 287, 1944. (119.) White, B.: *The Biology of Pneumococcus*, New York, Commonwealth Fund, 1938. (120.) Wollstein, M.: *J. Exp. Med.*, 20, 201, 1914.

(121.) Zinsser, H., Enders, J. F., and Fothergill, L. D.: *Resistance to Infectious Diseases*, 5th ed., New York, Macmillan, 1939.

PATHOLOGY AND BACTERIOLOGY

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THE SPREADING FACTORS AND BACTERIAL INFECTION

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It is rather striking that in our interest in the processes involved in bacterial infection we have become so preoccupied with those factors, both cellular and humoral, which have been thought to lead to success or failure in combating such infections that the study of the site at which these factors exert their effect has been almost completely disregarded as being of minor significance. Surely the rôle of the connective tissue must be an important one in any final result because it is either a barrier that must be crossed or a pathway if pathogenic microorganisms are to advance from their point of entrance to more vital tissues.

In 1942 this neglect of a fundamental consideration in the study of the nature of bacterial infection was pointed out and its significance stressed in a most able review of the problems of connective tissue permeability by Duran-Reynals.^{4b} It was appropriate that Duran-Reynals should draw attention to this concept, because his work stimulated the development of a new approach to the study of the mechanism of bacterial invasion of body tissues. Any such advance is to be welcomed because it is clear by now that the forces involved are more complex than originally appreciated and that a total understanding of what is involved can only come by a utilization of all available techniques as developed in both biological and physical sciences.

Before attempting to review our present knowledge as to the properties, nature and significance of spreading factors in bacterial infection, some consideration should be given to the position held by the connective tissue in this problem. In this connection the opinion that the ground substance of the connective tissue is a viscous substance offering resistance to the penetration of foreign materials, including bacteria and their products, would seem a reasonable one. It is also the opinion of Duran-Reynals and others that the permeability of the connective tissue is subject to variations which will in turn influence the ability of bacteria and other pathogenic matter to pass this barrier. While this permeability of the connective tissue is influenced by a number of diverse factors such as the age and race of the host and the area of the body concerned, as was pointed out by Duran-Reynals in 1936,^{4f} it is now held by many that of all factors increasing this permeability those designated by the term "spreading factors" are the most important. On this basis there is reason for considering the action of such spreading factors as being of comparable importance to phagocytic cells and antibodies in the field of resistance, or lack of it, to bacterial infection.

The original discovery of the spreading factors and their present identification with enzymes capable of hydrolyzing hyaluronic acid has been the result of the

coming together of two apparently unrelated studies. During the course of experiments on the effect of inoculation of vaccinia virus in rabbits it was observed that infection would develop most rapidly and with greatest certainty when inoculation was made into the testis of the animal. This was reported in 1929 by Stewart and Duran-Reynals.²¹ At this time Duran-Reynals also published reports^{4a,b} in which he demonstrated that vaccinia virus infection of the rabbit was more effective when inoculated into the skin along with aqueous extracts of rabbit, guinea pig or rat testicle. It did not matter whether the testicular extract was injected along with the virus or was injected intradermally some time previously in the area selected for inoculation. This action of testicular extract in enhancing the virulence of the infecting agent was then shown to be the result of an effect exerted upon the host tissues and not upon the virus itself as could be proved by the fact that the virus recovered from such lesions showed no alteration in its infectivity. This fundamental discovery was soon followed by other studies using various infectious agents in several species of animals and in 1930 it was reported independently by McClean^{8a} and by Hoffman and Duran-Reynals^{7a} that this effect of testicular extract was due to an increased tissue permeability. The term spreading factors was applied to substances having this property and their occurrence in such varied sources as invasive bacteria, poisonous insects and snake venoms was described.^{4c,g} In this connection it is interesting to note that observations have been reported^{1,4c,16} concerning the presence of a spreading effect from tumor extracts when tested with vaccinia virus, India ink and diphtheria toxin. These reports are in agreement as to this effect, but they show disagreement as regards the spreading effect of a particular type of tumor. The original method employed in the study of spreading factors was to make intradermal injections of a material thought to contain the spreading factor plus an indicator, such as India

ink, and to compare the spread of the inoculum with a control mixture. Since that time studies of the spreading factors in various tissues have been carried out and this effect is now reported for striated muscle, fasciæ, tendons, and gastric subserosal and subcutaneous connective tissues.

While this progress was being made on the mechanism of spreading factors, another series of investigations were being carried out in an apparently separate field. This work had to do with the nature of the ground substance in which the cells and connective fibers of the connective tissue are embedded. This matrix was generally assumed to be a protein of the "mucin" type, but protein-digesting enzymes such as trypsin are not spreading factors. In 1934 Meyer and Palmer¹¹ reported that the gelatinous fluid in vitreous humor is a kind of polysaccharide which they named hyaluronic acid. This discovery was followed in 1936 by a report by Meyer, Dubos and Smyth¹² that mucolytic enzymes could hydrolyze hyaluronic acid. Then in 1939 Chain and Duthie^{2a} described the existence of a mucolytic enzyme in testicular extract which a year later they^{2b} felt was identical with "spreading factor" and to which the term hyaluronidase was applied. In this manner two series of independent investigations were found to have a common bond of interest.

The acceptance of the identity of spreading factors and hyaluronidase is not complete. Duran-Reynals for example is inclined^{4h} to place under the designation of "spreading factors" all those substances produced by living organisms which have the common property of increasing the permeability of the connective tissue. Under this inclusive definition spreading factors would tend to fall into two main groups. In one group would be placed those factors with spreading power *in vivo* and an enzymatic effect upon hyaluronic acid *in vitro*. In the second group would be substances, such as ascorbic acid, which have spreading power but which exert no

enzymatic activity on hyaluronic acid. At the present time the consensus is that the true spreading factors are those of the first group. These are the product of the simplest organisms to the more complex; they are very soluble in water; powdered preparations may remain active for years; they are destroyed by heating at 60° C. for 30 minutes;^{7b} their effective permeability dose may be as small as 5×10^{-4} microgram;^{8b} and in their action *in vitro* they are specific and only hyaluronic acid or its sulphuric acid ester from mesodermal structures is attacked. For these reasons it seems proper to regard the spreading factors as enzymes identical with the hyaluronidases.

The interest at present aroused in the antigenicity of enzymes, as exemplified in the studies of Seastone and Herriott¹⁹ and of Sevag,²⁰ has focussed attention on this aspect of bacterial spreading factors. In 1932 Duran-Reynals reported^{4d} that immune serum prepared in the rabbit against testicular extracts would precipitate the extracts, suppress their spreading power and neutralize their ability to enhance vaccinia virus infection. A more recent study by McClean^{8c} showed that serum prepared against bull's testis inhibited this enzyme but did not inhibit a testicular enzyme from the mouse or any of the bacterial enzymes tested. This evidence of species specificity was in agreement with the results of other studies by the same author. In 1936 he had shown^{8b} that whereas an immune serum could be prepared against *Clostridium welchii* which would inhibit the diffusing factor of that organism; it had no inhibitory activity against testicular extracts. Later studies by McClean and Hale⁹ and by McClean^{8c} have shown that antihyaluronidase serum would neutralize the activity of the enzyme in a specific manner and that immune sera prepared against enzymes obtained from *Cl. welchii* and *Cl. septicum* are species but not type specific, whereas those obtained against streptococcal enzymes are group but not type specific. Since the diffusing activity of these en-

zymes in the skin will occur at a much higher dilution than that at which any *in vitro* viscosity-reducing activity could be demonstrated and because the immune sera prepared against hyaluronidase was able to inhibit completely only a limited number of minimal diffusing doses of spreading factor in the skin, Sevag²⁰ is of the opinion that this is the probable reason for the failure of some experiments to demonstrate inhibition of the spreading factor. The specific character of the inhibition of the spreading effect has led Duran-Reynals^{4b} to put forward two possible explanations for this phenomenon. On the one hand one can assume that the spreading factors are antigenic but quite different in even closely related species and this would indicate the presence of non-antigenic groups which would determine specificity. On the other hand one could speculate that the spreading factors are not antigenic and that the inhibition shown by immune sera is an accidental effect consequent upon a reaction with closely linked proteins which would inactivate the factors. The bulk of present evidence would appear to lend support to the first hypothesis.

Before considering the part that hyaluronidase may play in a specific bacterial infection, some discussion of the problem of invasiveness and/or, virulence is in order. With the majority of pathogenic bacteria in which invasive qualities are closely allied with virulence, we find that the characteristic picture of infection is one in which there is a well-recognized site of entrance into the body and a definite spread from that place. Staphylococcal, streptococcal and gas gangrene infections are of this order. In those infections in which the ability of the bacterial cells to cause disease is not so obviously allied with spread from a local portal of entry, we find that the invasion of the body tissues is one of dissemination by passive transfer from the respiratory or alimentary passages to those regions in which recognizable tissue changes occur, such as is the case in the majority of infections

caused by *Mycobacterium tuberculosis*, *Neisseria intracellularis* (meningococcus) and *Eberthella typhosa*. Studies^{4e,8b} that have been made concerning the production of spreading factor by individual bacterial species tend on the whole to be correlated with the significance that this property would appear likely to exert on the life history of a particular type of bacterial infection; but this correlation of spreading factor and invasive power is only a rough one at best and does not correspond to any other method of classification of pathogenic bacteria.

The part that spreading factor production plays in staphylococcal infections is very definite. Duran-Reynals^{4e} is of the opinion that *Staphylococcus pyogenes* can be further subdivided into groups on the basis of spreading factor production which will correspond to the quality and size of the lesion produced when these organisms are inoculated intradermally into rabbits.

The picture presented in streptococcal infections is not nearly so definite. In fact, while some strains of streptococci possess the spreading factor, others lack this ability and indeed the substrate to it (hyaluronic acid) is present in the capsule of some species. In 1944 Crowley³ reported a study of hyaluronidase production by hemolytic streptococci from human sources. She found that in 308 strains of Lancefield Group A organisms 64 strains, but from only two serological types (4 and 22), showed hyaluronidase activity; but in 68 strains of Groups C and G streptococci 48 strains showed this property. In this particular study all hyaluronidase-producing strains were non-capsulated. Earlier reports^{8d,13} had shown that it was possible to obtain an enzyme from the culture filtrates of some hemolytic streptococci which would lyse streptococcal capsules. While McClean^{8d} suggests that this enzyme is identical with the hyaluronidase produced by these organisms, Hobby *et al.*⁶ found that though some preparations from Group A hemolytic streptococci possessed both spreading factor and the ability to hydrolyze hyaluronic acid, preparations

from other Group A streptococci possessed the spreading factor but failed to hydrolyze hyaluronic acid. This leads to the conclusion that invasiveness of hemolytic streptococci involves factors other than hyaluronidase and may explain the divergence of opinion between Duran-Reynals,^{4e} who thought that the degree of invasiveness was largely determined by the amount of spreading factor, and Crowley³ who found no evidence that hyaluronidase-producing strains were associated with any particular type of infection or that hyaluronidase production is related to the virulence of streptococci for man.

The studies of Goodner^{5a,b} dealing with the production of skin lesions in the rabbit by the pneumococcus have shown that the injection of pneumococcal autolysates results in large spreading lesions and that such autolysates, from both homologous and heterologous types, would enhance the lesions produced in the rabbit by Type III pneumococci of varying pathogenicity.

In 1936 McClean^{8b} reported that the culture filtrates of certain pathogenic clostridia contained a spreading factor and more recently he¹⁰ has produced additional evidence to give substance to the claim that those clostridia which are characterized by their capacity for invasion of tissues are able to elaborate hyaluronidase. As a result of the study of the production of hyaluronidase by the clostridia, McClean, Rogers and Williams¹⁰ have made a novel suggestion concerning its possible use as a diagnostic procedure. It was appreciated that it might prove of considerable value to be able to demonstrate the presence of actively multiplying microorganisms before their presence can be detected by usual methods of clinical or laboratory examination. This is particularly true of gas gangrene infections where the need for early surgical interference is imperative. It was their belief that the demonstration of bacterial enzymes in the wound exudate would provide a means whereby this early diagnosis could be made. The work reported is purely ex-

PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF JANUARY 15, 1946

Absence of Antibodies in Granulocytes and Macrophages During Antibody Formation. W. E. EHRLICH, M.D., T. N. HARRIS, M.D., and E. MERTENS, M.D. (Philadelphia General Hospital, Children's Hospital, Philadelphia, and Depts. of Pathology and Pediatrics, Univ. of Penna.). A comparative study was made (1) of the relative agglutinin titers in the foot pads, the popliteal lymph nodes, and the blood serum of rabbits that had received injections into the foot of dysentery vaccine with or without paraffin oil; and (2) of the titers in the granulocytes and macrophages, and the supernatant fluid of the peritoneal exudates of rabbits injected intraperitoneally with various dysentery and typhoid antigen combinations. Although there was excellent antibody response, the exudates in the foot pads and the peritoneal cavity showed only insignificant quantities of agglutinin; in fact, the isolated granulocytes and macrophages of the peritoneal exudates revealed no agglutinin at all. As similar results were obtained by intravenous injection of antibody and subsequent introduction of a non-specific irritant, it was concluded that the low antibody titers at the sites of injection were due to secondary concentration here of antibody that was synthesized in the regional lymphatic tissue; there remained nothing to suggest that either the granulocytes or the macrophages were instrumental in the synthesis of the agglutinins studied.

The Fate of Particulate Antigens in Relation to the Formation of Antibody. T. N. HARRIS, M. D., E. MERTENS, M.D., and W. E. EHRLICH, M. D. (Children's Hospital of Philadelphia, the Philadelphia General Hospital and the Depts. of Pediatrics and

Pathology, School of Medicine, Univ. of Penna.). The fate of particulate antigenic material has been investigated, in the period between its injection into the foot of the rabbit and the appearance of antibodies in the regional lymphatic tissue.

It has been found that a soluble substance immunologically identical with the antigenic material injected can be identified in extracts of the injected tissue and of the regional lymph node, and in the efferent lymph from that node. The concentration of this soluble material falls off slowly in the injected tissue in the course of the few days following the injection. In the extract of the lymph node and in the lymph it falls off quickly, and is succeeded by the appearance of antibody.

Evidence is presented that this material is derived from the antigenic material injected by a physiologic process, and some quantitative implications are discussed.

Blood Flow in the Bronchial Artery of the Anesthetized Dog. H. D. BRUNER, M.D., and C. F. SCHMIDT, M.D. (Dept. of Pharmacology, Univ. of Penna.). Blood flow in the right bronchial artery was measured by the bubble flowmeter in 36 dogs anesthetized by pentobarbital or chloralose, in order to evaluate possible causal relations between this systemic blood flow and production of paroxysmal pulmonary edema. In 12 control experiments, flow was highest at the beginning of an experiment and decreased with decline of systemic pressure and cardiac output probably due to loss of heparinized blood. The average of the highest observed flows was 8.81 cc. per min., range, 1.1 to 26.7 cc. per min. The average maximal flow in 10 dogs ventilated by pump was

9.9 cc. per min. compared with 10.8 cc. per min. when breathing spontaneously. Several showed temporary cyclic or sporadic variations of flow without change of experimental conditions. In terms of simultaneous cardiac output, the extremes of flow were 0.03 % and 0.8 % of the cardiac output, and perhaps 50 % goes to extra-pulmonary structures; since the right lung is 1.25 times as heavy as the left, observed flow times 0.9 would represent approximately the order of flow which would drain into the pulmonary veins or enter the pulmonary artery capillaries on the respiratory bronchioles. Stimulation of the peripheral cervical vagus was followed by increased flow despite fall of systemic blood pressure, whereas stimulation of the peripheral cardiac branches from the stellate ganglion resulted in decreased flow despite raised systemic blood pressure. Acetylcholine, mecholyl, histamine, the xanthines, and nitroglycerine were dilator substances on intra-arterial injection, while epinephrine, ephedrine and posterior pituitary extract were constrictor. Atropine blocked the dilator action of acetylcholine, but only partially blocked that from cervical vagus stimulation. Ventilation with 7 % CO₂ resulted in a complex response, but the local effect of blood with this CO₂ content appeared to be dilator; a low PO₂ (7.5 % O₂) appeared to be weakly dilator in local action. The data are not consistent with the supposition that excessive bronchial artery flow is a direct cause of paroxysmal pulmonary edema.

Electrokymography Utilizing the Fluoroscope. W. EDWARD CHAMBERLAIN, M.D., BERT R. BOONE, M.D., and GEORGE C. HENNY, M.D. (Depts. of Radiology and Medical Physics, Temple Univ. Medical School and U. S. Public Health Service). The 931-A photo-multiplier tube, used with a recording galvanometer, will ac-

curately record variations in light intensity at the photo-sensitive surface of the tube. Such variations in light intensity may be produced in various ways from physiologic motions in the human or animal body. With proper application these motions are recorded with fidelity (Am. J. Roentgenol., 54, 217-229, 1945). For example, the motion of a selected point on the border of the fluoroscopic silhouette of a patient's heart may be recorded. This is done by placing a small piece of fluorescent screen directly over the light aperture of the photo-tube. The fluoroscopic Roentgen ray beam, after passing the selected part of the heart border, traverses a series of apertures in a simple arrangement of lead diaphragms and falls upon the fluorescent screen. The motion of the heart border produces variations in the amount of light emitted by the screen. Resultant variations in the electrical output of the photo-tube are readily recorded by a string galvanometer on moving bromide paper.

Other applications, with and without the fluoroscope, readily suggest themselves. For example, very successful plethysmographic records have been obtained.

Roentgen kymography has been used for the study of heart border motion but has failed to satisfy all of the requirements. Electrokymograms resemble electrocardiograms in detail and amplitude. Because they are accomplished with fluoroscopic Roentgen ray beams of conventional intensity, records of any desired length may be obtained. By simultaneous recording of the carotid pulse on the same strip of bromide paper as the electrokymogram, interpretation of the record of heart border motion is greatly facilitated. Experience suggests that electrokymography may find a field of usefulness in clinical cardiology as well as in physiologic and pharmacologic research.

BOOK REVIEWS AND NOTICES

PHYSICAL CHEMISTRY OF CELLS AND TISSUES. By RUDOLF HOBER, University of Pennsylvania School of Medicine, Philadelphia, Pa. Pp. 676; 70 ills. Phila.: Blakiston, 1945. Price, \$9.00.

In this volume physiology is considered "as a branch of physical chemical science dealing with life as a physical, though exceedingly complex system, that may be subjected to scientific analysis like any other natural object." The book begins with a discussion of the fundamentals of classical physical chemistry, commencing with atomic and molecular structures and graduating to more complicated aggregations of these basic units, such as the amorphous colloidal micellæ. Next, the structure of protoplasm is considered and the functional aspects of plasma membranes. Cell and tissue respiration, contractility, intestinal absorption, and the formation of urine are among the subjects treated. Of great interest is the discussion of the mechanism by which, in sub-microscopic cellular structures, the liberated energy can be utilized for the performance of work.

Dr. Hober is one of the best known workers and teachers at the Marine Biological Laboratory at Woods Hole and is a member of the Department of Physiology at the University of Pennsylvania. Dr. Hober was dismissed as President of the University of Kiel for his activity in opposing Nazism and his books were among the first to be burned.

This present volume is an excellent modern treatment of the subject, filled with stimulating ideas, and soundly objective concepts. It should be read by everyone engaged in work on the cell. D. C.

THE PSYCHOANALYTIC THEORY OF NEUROSIS. By OTTO FENICHEL, M.D. Pp. 703. New York: W. W. Norton, 1945. Price, \$7.50.

INSTEAD of complying with the request for a second edition of "Outlines of Clinical Psychoanalysis," the author has prepared the present book, which is only intended for

those who have undergone a personal analysis. No definite case reports are given but there are examples to illustrate different mechanisms. Part I: Preliminary Considerations: Introductory Remarks on Psychoanalysis and the Theory of Neurosis; The Dynamic, The Economic, and The Structural Point of View; The Method of Psychoanalysis; Early Mental Development: Archaic Ego; Early Mental Development (Continued): Development of Instincts, Infantile Sexuality; Later Phase of Development: The Superego. Part II: Psychoanalytic Theory of Neurosis: Traumatic Neuroses; The Motives of Defense; The Mechanisms of Defense; The Direct Clinical Symptoms of the Neurotic Conflict; Anxiety as Neurotic Symptom: Anxiety Hysteria; Conversion; Perversions and Impulse Neuroses; Depression and Mania; Schizophrenia; Defenses Against Symptoms, and Secondary Gains; Character Disorders; Combinations of Neuroses and Psychoneuroses; The Clinical Course of Neuroses; Therapy and Prophylaxis of Neuroses.

Indications for Psychoanalytic Treatment: hysteria, compulsion neuroses, and pregenital neuroses, "neurotic" depression, perversions, addictions, and impulse neuroses, psychoses, severe manic-depressive cases, and schizophrenics. Contraindications: the age, feeble-mindedness, unfavorable life situations, the triviality of neuroses, the urgency of a neurotic symptom, severe disturbances of speech, lack of a reasonable and coöperative ego, certain secondary gains, schizoid personalities, contraindications to analysis with a particular analyst. In the manic-depressive and schizophrenic groups, it is better for patients and for the benefit of science for psychoanalytic studies to be conducted in institutions. The very brief discussion on shock therapy states that such treatments should be administered after psychotherapy has proved unsuccessful. The book represents the most approved and advanced psychoanalytic thought. There is a bibliography of 74 pages. N. Y.

ELECTROTHERAPY AND LIGHT THERAPY.

With the Essentials of Hydrotherapy and Mechanotherapy. By RICHARD KOVÁCS, M.D., Professor of Physical Therapy, New York Polyclinic Medical School and Hospital, etc., New York. Pp. 694; 353 ills. Fifth ed. Phila.: Lea & Febiger, 1945. Price, \$8.50.

THIS edition is a triumph both for Kovács and the publishers. The first thing a reviewer notices about this new volume is the snugness with which it fits into the hand as compared with the bulkier volumes of former editions. In these days of acute shortages, it would be difficult to ascertain by what legerdemain of the book binding and printing arts this book has been produced. The excellent paper and the clarity of the print and illustrations make this book a joy to read. Incidentally, there are 38 more photographs and schematic drawings than in the previous edition.

The section on Static Electricity appears to be the only one that has been abbreviated. This seems unfortunate as the static machine is a valuable aid in the hands of one trained to use it. More physicians should emulate the late William Benham Snow, who obtained remarkable results with static electricity. It is true that the stigma of empiricism attaches to many of the treatments of physical therapy in the minds of many physicians, and this is well exemplified by the use or abuse of the static machine. However, many bio-physicists are endeavoring to set up standard methods of measurements and physical and physiologic bases for treatment. Kovács' expanded section on Newer Methods of Electro-Diagnosis and Electromyographic Diagnosis gives an indication of what is being attempted along the lines of measuring action potentials accurately. Investigations such as these will rid physical medicine of many of its rule-of-thumb methods.

Behrend's chapter on Exercise is also considerably enlarged, and there is an excellent review of the modern physical therapy treatment of infantile paralysis with an unbiased evaluation of Sister Kenney's methods. These two additions are welcome, as more careful attention should be paid to corrective exercises and muscle re-education.

A glossary in two parts has been added to this fifth edition. Part I is of terms used in Electrophysics and will prove valuable to

the physician and technician using electrical apparatus and for an understanding of the subjects of Electrophysics. Part II is of terms relating to Mechanotherapy and Muscle and Nerve Action.

It is not too much to say that no other book will so logically and easily induct the physician into the mysteries of medical electrophysics as this fifth edition of Kovács' *Electrotherapy and Light Therapy*. This volume ought to be in the library of every physician and is absolutely essential to physicians specializing in Physical Medicine and their technical aides. S. H.

AN INTRODUCTION TO PHYSICAL ANTHROPOLOGY. By M. F. ASHLEY MONTAGU, Associate Professor of Anatomy, Hahnemann Medical College and Hospital, Philadelphia; Visiting Lecturer, Department of Sociology, Harvard University. Pp. xiv, 326; 25 figs.; 6 tables. Springfield, Illinois: Charles C Thomas, 1945. Price, \$4.00.

THIS excellent little volume provides a most readable and stimulating approach to the subject-matter of physical anthropology. It is not intended to serve as a text nor a reference work for the specialist but rather as an introduction to a fascinating and important field. The general student, be he physician, anatomist, sociologist, or psychologist, will discover numerous facts and ideas in its chapters which should afford him an even deeper appreciation of his own particular subject. The text is systematic, well organized and clearly written and the tables and diagrams are ingeniously arranged and informative. The author is himself a well known anthropologist and anatomist and should speak with authority on the subject.

In the first 2 chapters definitions and general principles are discussed and a brief but systematic account is given of the primates as a zoölogical group. Chapter III deals with the origin and evolution of the non-human primates and provides a necessary background for an understanding of the more recent evolution of man himself. Evidence is given that the tarsoid group provided the material from which all later primates developed. Chapter IV is concerned with the advent of man himself and the fossil types, particularly the more recent discoveries, which point the way backwards along

the zigzag path into the past. Newer theories concerning present day man's evolution reflect considerable doubt upon the older concepts of linear evolution and attention is drawn to the almost certain admixtures which must have occurred between extinct *Homo sapiens* and other coeval human types in the past. Chapters V and VI give a progressive and scientific basis for an analysis of the various present day ethnic groups. Shibboleths and misconceptions of "race" are strongly debunked. True genetic criteria are rightly advocated as the only scientific means by which group affinities and descents may be ascertained. The last 2 chapters might be said to deal with the

scientific ideology which should furnish the basis for any true and proper evaluation of the physical and mental "protuberances" of man, taken individually or in groups. An appendix gives some of the more common methods and procedures used in anthropometry.

A rudimentary acquaintance with the principles of anthropology will do no one any harm, least of all the doctor. Alarming misconceptions held by many medical students concerning both fact and fancy of race, have convinced the reviewer (himself no anthropologist) that this book should be required reading for every would-be physician.

J. P.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

APRIL, 1946

ORIGINAL ARTICLES

THE COURSE OF FILARIASIS AFTER REMOVAL FROM AN ENDEMIC AREA

BY CAPTAIN ALTON W. BEHM, M.C., A.U.S.

AND

COLONEL JOSEPH M. HAYMAN, JR., M.C., A.U.S.

SWANNANOA, NORTH CAROLINA

(From the Tropical Disease Section, Moore General Hospital)

DURING the past 2½ years a number of reports on the early manifestations of filariasis have appeared.³ These in general have been based on the results of the examination of troops in endemic areas or of those evacuated because of the diagnosis of this disease. They have provided new and important information on the incubation period and initial symptoms of infection with *W. bancrofti* in young adult while males.

It will, of course, be a number of years before final appraisal can be made of the results of exposure of troops in endemic areas. It seems worth while, however, to present an "interim report" on the history and condition of 532 men 2 years after leaving the island Tonga-tabu, a highly endemic area, where they had been on duty from May 1942 to May 1943. A report of the symptoms which developed in these men in the latter part of 1943 has already been published.⁵

In addition to these men, who will be referred to as Group A, 2 groups of replacements had been evacuated with them. The larger of these, consisting of 145 men (Group B) had joined the units after Group A had left Tonga-tabu, but were stationed with them for 6 months in 1943 on Woodlark Island, one of the Trobri-

ands, which lie off the eastern end of New Guinea. While this island is in the filarial zone, and the disease presumably exists among the natives, as far as can be ascertained from medical officers who were stationed there it is at least uncommon and no record of a native infected with filaria has been uncovered. Yet, as will be shown, the men in Group B developed the same symptoms as those in Group A, and at the same time. Group C comprised 32 men who were late replacements and had never been in an endemic area.

While complete medical histories have not been available, the notes of the Battalion Surgeon for the larger element of the groups after they had reached Woodlark Island, and the results of a survey for filariasis made at a general hospital overseas in January 1944 have been most helpful.^{1a} The 532 men forming the basis of this report do not constitute the total number exposed on Tonga-tabu. Some had been evacuated from Woodlark or Australia with the clinical diagnosis of filariasis, or for other reasons, before coming under our observation.

Since microfilariæ in the peripheral blood or adult worms in biopsy material have been demonstrated in only a very small number of these cases, it has been

necessary in the majority to make the diagnosis solely on clinical grounds. In the absence of repeated observed attacks of lymphadenitis, retrograde lymphangitis, or scrotal swelling for which no other cause can be found, in an individual known to have been in an endemic area, the diagnosis of filariasis is difficult and often must be uncertain. Emphasis is placed on observed physical findings, because men who have seen elephantiasis among natives, and who have been subjected to repeated questioning and examination, very naturally have developed pronounced anxiety concerning the effect possible infection in them may have. They have tended to exaggerate symptoms and to worry about every minor twinge or discomfort in arms, legs or scrotum, no matter what the cause. Rome and Fogel⁹ called attention to this understandable emotional overlay, to which the admitted lack of knowledge by medical officers at the time of the course and possible sequelæ of this disease contributed. Factual knowledge was necessary for the proper handling of these men. Augustine¹ has recently stated his belief that "the evidence at hand is insufficient to warrant making a diagnosis of bancroftian filariasis on all cases from the South Pacific in which lymphadenitis, lymphangitis or suggestive genital signs may have occurred."

The early symptoms of filariasis as observed in troops have consisted of attacks of lymphangitis, lymphadenitis, funiculitis, epididymitis and swelling of the testicles. These attacks usually last from 3 to 5 days, occasionally 10 days to 2 weeks, and rarely as long as a month. In a fair proportion of cases the attack is preceded by malaise, and accompanied by fever, usually low, but occasionally as high as 103° to 104° F. With the subsidence of the attack, the pain disappears and the swelling diminishes, although palpable enlargement of lymph nodes or palpably thickened lymphatics may persist. The lymphangitis is the most striking and characteristic feature of these attacks. In contrast to the usual lymphangitis of

bacterial infection, it is retrograde, proceeding in the course of 1 to 3 days from the axilla down the arm toward the elbow, or from the epitrochlear or antecubital region down the forearm to the wrist and hand. This lymphangitis is manifest by red linear streaks, palpable lymphatic vessels, and edema without local heat. In the lower extremity it progresses from the inguinal region down the inner aspect of the thigh or, quite characteristically, around the lateral aspect of the thigh, above the greater trochanter, to the gluteal region.

On admission of these men to the hospital, in addition to a routine medical history, special questions concerning itinerary, living conditions, contact with natives, type of duty, symptoms of possible filariasis, with dates and recurrences, were asked and recorded on work sheets. During the physical examination special attention was paid to palpable lymph nodes, lymphangitis, and abnormalities of the scrotum and its contents. In addition to the routine blood count, Kahn test, urine and stool examination, the blood of each man was examined repeatedly for microfilaria, both day and night, in thick smears and by Knott's method, using 1 to 20 cc. of blood. Intradermal tests with an extract of *Dirofilaria immitis* were carried out according to the technique of Bozicevich and Hutton.

Only 83 men (15%) of Group A denied all symptoms suggestive of filariasis. One-quarter of the group (133) believed that they were physically able to do full duty, while 24 (4.5%) felt themselves incapacitated by the disease for any type of duty. The remaining 373 (70.5%) believed that they could do only some type of limited duty. There were 252 (47.3%) who claimed that exercise produced symptoms, 77 that hot weather made them worse. Thirty-three believed their sexual potency to have been impaired. The opinion of the men in the other groups was not very different; 52.4% of Group B believed themselves fit only for light duty, and only 44.8% did not complain of symptoms sug-

gestive of filariasis. It is noteworthy that in the small Group C composed of men who had never been exposed, 8 men (25%) believed that they could only do light duty, while 2 believed that they were totally incapacitated for any type of duty by filariasis. These facts bring out the importance of psychologic factors and anxiety in men among whom a new and little understood disease appears.

During the period of exposure the men had lived in unscreened tents, but were provided with mosquito nets for sleeping. Contact with natives is said to have been

dence remaining low, however, during the first year, and increasing sharply some 14 months after first possible exposure while they were stationed on Woodlark. None of the symptoms occurring during the year on Tonga-tabu were recognized at the time as due to filariasis. The time of initial symptoms is shown in Figure 1. This "incubation" period is similar to that reported by King³ and others. It is not an accurate picture of the group, however, since it does not include the men, something in excess of 60, who had been evacuated separately and were not available for

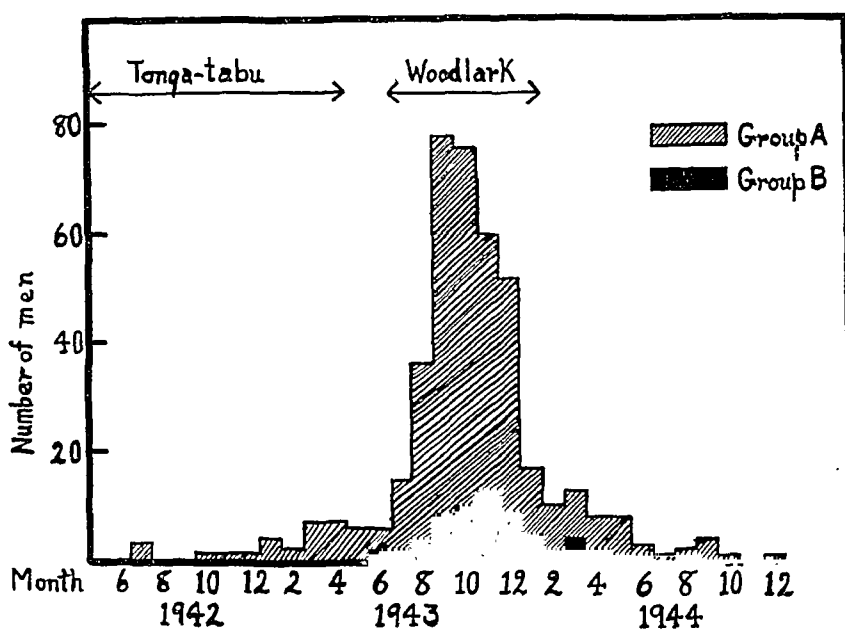


FIG. 1.—Date of first symptoms suggestive of filariasis.

common. The filariasis on Tonga-tabu is of the non-periodic type, that is, among natives *microfilariae* can be found in the peripheral blood during both day and night. The common vector is said to be *Aedes scutellaris*. There was no difference in the incidence of symptoms among men whose duties had been in the jungle, on patrol, etc., and cooks, clerks and others, whose duties had been chiefly around camps.

According to the histories given by Group A, the first symptoms suggestive of filariasis developed between 2 and 3 months after the first exposure, the inci-

study. Also shown in Figure 1 is the time of onset of symptoms of 62 men in Group B in whom this could be dated. If this was filariasis in Group B, symptoms began to develop in less than 2 months after first possible exposure, and reached a maximum incidence in 5 months instead of 17 to 18 months as in Group A.

The site of the initial attack in Group A, as obtained from the histories, is shown in Table 1. Subsequent attacks involved the same area as the original or another region. That is, 1 man would give a history of repeated swelling of the epitrochlear nodes in one arm, while in another the initial

involvement might be in the scrotum, and the 2d attack involve the lymphatic structures of the arm. A summary of the areas involved in all attacks is shown in Table 2.

TABLE 1.—SITE OF INITIAL SYMPTOMS
IN GROUP A

Scrotal swelling	105
Axillary adenitis	28
Epitrochlear adenitis	30
Inguinal adenitis	63
Cervical adenitis	9
Multiple sites	121

TABLE 2.—INCIDENCE OF INVOLVEMENT IN
REPEATED ATTACKS IN GROUP A

Scrotal swelling	262
Axillary and epitrochlear	187
Inguinal and femoral	161
Cervical	21

A history of the number of attacks experienced was difficult to obtain. Some men gave excellent accounts of clear-cut attacks. Others claimed that they had never been free from symptoms since onset. The majority of these, however, showed no demonstrable physical abnormality. Omitting such cases, the number of attacks varied from 1 to 12. The distribution is shown in Table 3.

TABLE 3.—NUMBER OF ATTACKS OF LYMPHADENITIS, ADENITIS, OR GENITAL INVOLVEMENT

No. attacks	Men
1	139
2	99
3	76
4	53
5	21
6	10
7	1
8	2
10	3
12	3
13	1

The results of physical examination in September 1944 are shown in Table 4. Any palpable epitrochlear or axillary lymph nodes have been recorded. Small, discrete, non-tender inguinal glands, which would be graded 1 plus on a scale in which a gland 1 cm. in diameter would be called 4 plus, have not been recorded.

No microfilariae were found in the peripheral blood of any of these groups while at the hospital. Microfilariae had been repeatedly demonstrated, however, in one

man of Group A while on Woodlark, and in a second before arrival at this hospital. Neither of these men were available for study. In addition to these 2, the records of 2 other men of Group A recorded the finding of a single microfilaria on one examination. These two were examined repeatedly over a period of several months, but no microfilariae could be found.

TABLE 4.—POSITIVE FINDINGS ON PHYSICAL
EXAMINATION IN GROUP A

Axillary adenitis	167
Epitrochlear adenitis	62
Inguinal adenitis	272
Femoral adenitis	167
Enlarged epididymis or testicle	34
Thickened cord	63
Chronic lymphangitis	5

Biopsies of lymph nodes had been performed on 13 men before they came under observation at this hospital. Adult worms were found in sections from 2 cases. We performed biopsies in 7 other cases; in 1 a microfilaria was found in a thrombosed lymphatic.

These entire groups were kept under observation for from 2 to 10 months. During this period a number developed attacks of lymphadenitis, lymphangitis, or scrotal swelling, believed due to filariasis. Some attacks developed spontaneously, the majority were precipitated by exercise. The incidence and severity of attacks diminished with the time since leaving the endemic area. The relation of the time of last attack and removal from the endemic area is shown in Figure 2. All patients were subjected to a month's intensive training without symptoms before being regarded as free from attacks. Many men complained of pains in arms or legs, unaccompanied by swelling, after exercise. Since the pathology of early filariasis is either the result of lymphatic obstruction or an allergic reaction to the liberation of antigen from adult worms, it is believed that a complaint of pain without swelling is more properly interpreted as due to muscle strain, fatigue, arthritis, neuritis or some other cause rather than filariasis.

In Group A, a "definite" clinical diagnosis of infection had been made in 104

men in the fall of 1943 while they were still on Woodlark Island and a "possible" diagnosis in an additional 68. A "definite" clinical diagnosis had also been made in 10 men in Group B, and a "probable" diagnosis in an additional 4. The conclusions of the survey made by a General Hospital overseas in January 1944 was that 67.8% of Group A were presumably infected, and that there were suggestive symptoms in another 24.7%, leaving only 7.5% believed to be free from suspicion of infection. In Group B, 21.1% were believed to be infected, and infection probable in an additional 29.4%.

effort to eliminate false positive reactions Bozicevich and Hutter² used a 1:8000 extract instead of the 1:1000 used by Taliaferro and Fairley and in addition used a control of the same dilution of dog serum protein.

Bozicevich and Hutter reported no false positives in men who had never been in an endemic area. Using their technique 2 of 32 men, or 6% in Group C gave positive reaction. King, using a 1:1000 antigen prepared according to Fairley's technique, got 10.5% positive reactions in 171 controls. Using the same antigen, the overseas General Hospital referred to

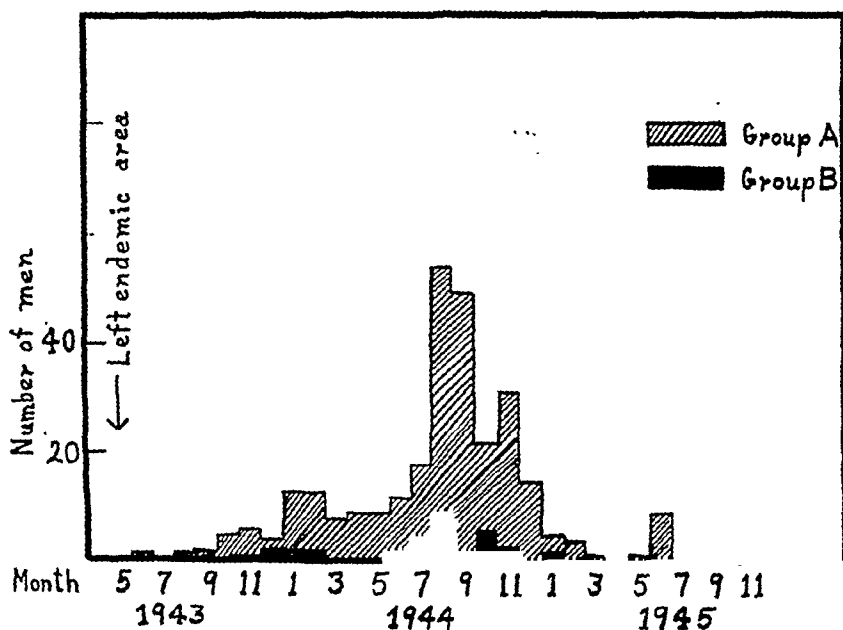


FIG. 2.—Date of last attack suggestive of filariasis.

It would, of course, be extremely helpful to have some reliable laboratory test which would either exclude filarial infection, or if the error consisted of false negative reactions, could be trusted to establish it. The most promising of such tests is the skin test. Unfortunately, antigens prepared from *W. bancrofti* are not available. Those that have been used are prepared from other filarial worms, most work having been done with extracts of the dog heart worm, *D. immitis*. This test was developed independently by Taliaferro and Hoffman¹¹ and by Fairley.⁴ In an

above obtained 11% positive reactions in 100 men recently arrived from the United States, and 18% in 72 men without symptoms but who had had some service in New Guinea in an area in which filariasis has not been recognized among troops. The results of skin tests in Groups A, B and C are given in Table 5.

TABLE 5.—PERCENTAGE POSITIVE SKIN TESTS WITH *D. IMMITIS* ANTIGEN

	Feb-March 1944 1:1000	Sept. 1944 1:8000
Group A . . .	73.9	57.7
Group B . . .	27.9	18.3
Group C	6.0

These results pose some problems in interpretation. The positive reactions in Group C may be accepted as "false positive," and is the same order of frequency as that obtained by King although higher than by Bozicevich and Hutter. The slightly higher incidence (10.5 to 11%) obtained with 1:1000 antigen in control series mentioned above may be attributed to the greater amount of protein injected.

Many of the men giving positive skin tests in Group A had had no symptoms of the disease during the 17 months after leaving the endemic area nor during the year of exposure. Such reactions might be thought of as due to a "biological" rather than "clinical" infection; that is, to an infection sufficient to produce skin sensitization but no symptoms, comparable to that observed in certain individuals who give a positive reaction to trichinella antigen. But it is hard to apply this explanation to the incidence in Group B (3 times control series) where the possibility of infection is problematical, and to the rate observed in New Guinea troops (1.6 times control series). Attempts to relate this increased incidence to coincident infection with intestinal helminths have been unsuccessful. At present we have no explanation for this apparent increased skin sensitivity in those who have had tropical service, but it is obvious that it makes the skin test of less value in Group A than is desirable.

Here, then, was a group of over 700 men who were non-effective because of the demonstrated presence of filariasis in a few of them, suggestive physical findings in others, and symptoms without findings but with manifest fear of the disease and anxiety in many more. Others who had been completely symptom-free showed positive skin tests to *D. immitis* antigen. Under current directives those in whom the diagnosis was made were classed as fit only for duty in the Zone of Interior. Since the emotional and psychologic effects of a positive diagnosis was usually much more incapacitating than the manifestations of the disease, and since a positive

diagnosis could be made at any time on development of sufficiently characteristic symptoms, it seemed proper to regard only those persons as infected with filaria who presented either a characteristic history of repeated attacks of "mumu," or demonstrable physical signs. Weight was given to a positive skin test, but it alone was not regarded as sufficient for a positive diagnosis. On the other hand a negative skin test did not exclude a diagnosis of filariasis.

After the completion of examination, laboratory studies, and the response to reconditioning, each man's case was appraised. A diagnosis of filariasis was made in those who developed lymphadenitis, especially epitrochlear, axillary, or femoral or funiculitis, epididymitis or orchitis under observation. A retrograde lymphangitis even in the absence of other findings was considered sufficient. A positive diagnosis was also made on a history of one or more clear-cut attacks of "mumu," with swelling, lasting for a day or longer. A history of attacks of pain without swelling, of swelling lasting "a few minutes," of pain in muscles without swelling, or of slight bilateral inguinal adenopathy coming on after a long hike and disappearing with further training, was not considered adequate evidence of filariasis to justify a diagnosis. Nor was the presence of small non-tender axillary, inguinal or femoral glands, which had never given rise to symptoms regarded as acceptable. Such adenopathy was found to be so extremely common by one of us in hospitals in New Guinea as to be of little significance in diagnosis.

A diagnosis of filariasis was made in 196 men (36.8%) in Group A. Of these, 3 were separated from the service because of filariasis—1 with persistent lymph edema of both legs, and 1 with a lymph scrotum, and 1 with recurrent lymphangitis.

A diagnosis of filariasis was also made in 6 men in Group B on the basis of a typical history of "mumu" although no attacks were observed and all had negative skin tests. With the information now available of the questionable presence of a signifi-

cant amount of filariasis on Woodlark Island where they served, it is believed that these diagnoses were incorrect.

Twenty-eight men of Group A were separated from the service or placed on limited duty for other reasons. The remaining 308 were returned to duty as not infected with filaria. Of these, 5 have returned to the hospital for further observation. One of these had had a very equivocal history, negative physical examination, and repeatedly negative skin tests. On re-examination he complained of pains in arms and axillæ without demonstrable swelling, skin test was again negative, and he was again discharged to duty. It is believed that his symptoms are entirely on a functional basis. Another

ciently typical symptoms on re-examination to justify the diagnosis of filariasis in spite of repeatedly negative skin tests. In addition to these men, 6 men of Group A and one from Group C have reported on sick call at their present post complaining of swelling of inguinal or, in 1 case, axillary glands. These were not incapacitating and the men returned to duty. Thus follow-up for an additional 8 months has led to a change in diagnosis in approximately 1%.

The histories, physical findings, and skin tests of Group A were again reviewed and separated into those diagnosed as filariasis and as not filariasis. The results, together with similar data for Group B, are shown in Table 6. When the data are

TABLE 6.—INCIDENCE OF POSITIVE HISTORY, PHYSICAL SIGNS, AND SKIN TEST ACCORDING TO DIAGNOSIS

	Group A		Group B
	196 men filariasis (%)	336 men not filariasis (%)	145 men not filariasis (%)
History of swelling arms	55.1	23.5	13.3
legs	42.8	22.9	20.6
scrotum	73.4	35.2	23.4
Axillary adenopathy	49.4	20.8	23.4
Epitrochlear adenopathy	23.9	4.4	4.1
Inguinal adenopathy	75.5	36.6	34.5
Femoral adenopathy	50.5	20.2	19.3
Enlarged epididymis or testicle	14.2	1.7	1.3
Thickened cord	21.9	5.6	5.5
Cervical adenopathy	2.0	1.4	
Positive skin test	79.5	42.0	19.1

had been admitted to a Station Hospital complaining of pain without swelling in the testes, and pain without swelling in the right thigh. Shortly after admission, he developed infectious hepatitis. On transfer to this hospital he showed only small discrete, non-tender inguinal glands. He was observed for an additional 3 months, including 2 of strenuous reconditioning without further symptoms. It was believed that he did not present sufficient evidence of filariasis to justify the diagnosis, and he was again discharged to duty. Two men had had suggestive histories and positive skin tests when first examined, and on re-examination presented demonstrable adenopathy and were discharged as filariasis. The 5th man showed suffi-

assembled in this way, the incidence of a history of swelling of arms, legs or scrotum, and the incidence of positive physical findings in the "not-filariasis" men in Group A and in Group B is strikingly similar. The greater number having positive skin tests in Group A may be an expression of the "biological" infection referred to above. The number of definite attacks of "mumu," so far as could be ascertained, in the 3 groups is shown in Figure 3.

Comment. What the future holds for those in Group A who have been infected cannot be predicted with certainty. From Figure 2, it is apparent that the incidence, as well as the severity, of symptoms has rapidly diminished during the past year.

O'Connor and others have reported patients who on return from an endemic area lived the rest of their lives without symptoms. Will these men show microfilariae in the peripheral blood at a later date? In India, Ivengar⁶ found that the incidence of filarial infection (microfilaria in blood) increased from childhood up to the age of 20, and then remained constant, while the incidence of filarial disease, as manifest by symptoms, increased steadily up to the age of 45. That is, microfilariae were less apt to be found in the blood of those showing symptoms than in those symptom-

sated for by a ripe anastomosis. The embryos give rise to no trouble, but circulate as easily as blood corpuscles. When in health and not disturbed, they are perfectly innocuous." That the lymphadenitis and lymphangitis of filarial disease are not fundamentally due to secondary bacterial infection has been shown by O'Connor,⁸ Wartman¹² and others. These symptoms are in the nature of an allergic response on the part of the host to some antigen derived from dead or living worms, and therefore indicate some degree of immunity. Biopsies of acutely swollen glands and

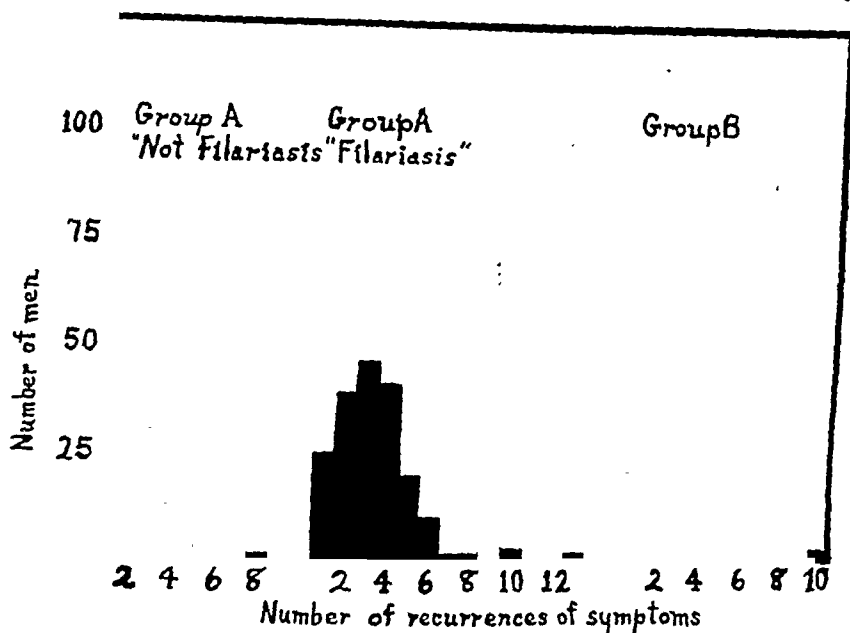


FIG. 3.—Frequency graph of number of attacks of "mumu."

free. This has also been corroborated in many other surveys. Manson⁷ in 1883 wrote of Bancrofti infection: "There is nothing in it, or its relation to the human host, incompatible with the perfect health of the latter. The amount of injury done to the lymphatics by the minute, immature parasite in its travel toward its permanent abode is so trivial that no serious disease can possibly result from it. The mature animal itself lies extended in a vessel and is perfectly adapted by size and shape for the situation it occupies. It creates no irritation and the small amount of obstruction it may give rise to is readily compen-

lymphatics have shown both dead, disintegrating and mature, living worms. Thus even in these early cases some worms are already dead. Others are apparently producing mature microfilariae. The hypothesis that the failure to demonstrate microfilariae in the peripheral blood is due to obstruction in glands or lymphatics, and that with the passage of time channels may be opened permitting access to the vascular system appears unlikely. The most obvious explanation for the failure to find microfilaria is the minimal or light infection. It also seems reasonable that some worms will continue to die, and that the

few survivors will live in the innocuous symbiosis described by Manson. With few exceptions it therefore seems reasonable to predict that those men who have these minimal infections will have little further physical disability and less incapacity. Zeligs¹³ has presented convincing evidence for this conclusion from a large experience with similar cases of filariasis at the U. S. Marine Barracks, Klamath Falls, Oregon.

One soldier, who served in another endemic area, has been encountered, who has never had any symptoms but shows large numbers of microfilariae in his blood. It is believed that this, however, is very exceptional, and cannot be used to support the suspicion that a condition may exist among troops similar to that found by Ivengar among natives in India, namely a high incidence of filarial infection without symptoms. If this were so, it is reasonable to suppose that microfilariae would have been found in the repeated searches in the symptom-free members of Group A. Such, however, was not the case.

A considerable number of troops stationed in certain parts of the Pacific area have been infected with filariasis during this war. Due to the unfamiliarity of most physicians with the early manifestations of the disease, the diagnosis has been made not only in men who have never been in an endemic area, but in many others whose symptoms were due to a variety of causes. Men have been sent to this hospital with a diagnosis of filariasis who suffered from angioneurotic edema, thrombophlebitis, lymphogranuloma venereum, epididymitis secondary to prostatitis or urethritis, and a variety of similar conditions. In our opinion the occurrence of muscle pains, nocturnal orchiodynia or numbness in an extremity, even in men who have been in an endemic area, is not evidence of filarial infection.¹⁰ Too much emphasis cannot be laid on the fear, worry, and anxiety produced in men when the suggestion of possible filarial infection is made. There is fear of a slowly developing, disfiguring and ultimately incapacitating disease. Anxiety for loss of potency or fertility and the

possibility of carrying on a normal family life is often extreme. The fact that no specific effective treatment, other than time, has yet been accepted adds to the sense of helplessness and abandonment. Zeligs has presented factual data which shows that these fears are groundless. His data and ours show that in a non-endemic area the disease filariasis burns itself out after one or more reactivations. The longer the period of inactivity because of a diagnosis of filariasis, the more difficult it is to return men to duty. When presented with evidence of their ability to lead normal lives, and the demonstration that they can exercise without producing symptoms most men cease to be concerned. Those with a past history of psychoneurotic behavior, or where the element of secondary gain from light duty was prominent, frequently used filarial symptoms to help solve pre-existing emotional problems or to escape unpleasant situations.

The diagnosis of early filariasis is difficult. Demonstration of microfilariae or adult worms in biopsy material are the only documentary evidence. The observation of a typical attack of "mumu," with fever, lymphadenopathy and retrograde lymphangitis is convincing. In patients removed from an endemic zone, where diagnosis must be based on history, symptoms, and minimal physical findings, a careful appraisal of all evidence is essential. The skin test is helpful, but eosinophilia or other laboratory examination is of no value. It must be determined whether the man has been in an endemic area. All other discoverable causes for the symptoms should be excluded. The emotional status of the patient must be appraised. When a diagnosis of filariasis is made, sufficient factual data is now available to provide a favorable prognosis. Simple rest for a few days during acute exacerbations, with a prompt return to duty is the proper treatment.

Summary. 1. Observations are reported on 532 men who had spent a year on an island where filariasis was highly endemic.

Sufficient clinical evidence was present to make a clinical diagnosis of filariasis in 36.8%. *Microfilaria* were demonstrated in at least 2, and possibly 4, men who had been stationed on this island. Persistent disabling symptoms were present in 3. The recurrence of symptoms, usually precipitated by exertion, diminished with the

passage of time. Most men were symptom-free after they had been out of the endemic area 20 months.

2. Observations are also reported on the symptoms and physical findings in 145 men among whom clinical diagnoses had been made, but in whom exposure was problematical.

REFERENCES

1. AUGUSTINE, D. L.: Filariasis, New York State J. Med., 45, 495, 1945.
- 1a. BROWN, T. MCP., BETHEA, JR., W. R., and STIFLER, JR., W. C.: Early Filariasis, Bull. Johns Hopkins Hosp. (To be published.)
2. BOZICEVICH, J., and HUTTER, A. M.: Intradermal and Serological Tests With *Dirofilaria immitis* Antigen in Cases of Human Filariasis, Am. J. Trop. Med., 24, 203, 1944.
3. DICKSON, J. G., HUNTINGTON, R. W., and EICHOLD, S.: Filariasis in Defense Forces, Samoan Group, U. S. Naval Med. Bull., 41, 1240, 1943. MICHAEL, P.: Filariasis Among Navy and Marine Personnel: Report on Laboratory Investigations, U. S. Naval Med. Bull., 42, 1059, 1944. FOGEL, R. H., and HUNTINGTON, R. W.: Genital Manifestations of Early Filariasis, U. S. Naval Med. Bull., 43, 263, 1944. JOHNSON, P. A. G.: Filariasis, Clinical Findings in 189 Cases, U. S. Naval Med. Bull., 43, 940, 1944. KING, B. G.: Early Filariasis, Diagnosis and Clinical Findings, Am. J. Trop. Med., 24, 285, 1944. ENGLEHORN, T. D., and WELLMAN, W. E.: Filariasis in Soldiers on an Island in the South Pacific, AM. J. MED. SCI., 209, 141, 1945. BYRD, E. E., STAMANT, L. S., and BROMBERG, L.: Studies on Filariasis in the Samoan Area, U. S. Naval Med. Bull., 44, 1, 1945. GLASNER, F.: Filariasis in Returning Marines, U. S. Naval Med. Bull., 44, 21, 1945. SMITH, F. R., JR.: Filariasis: A Study of 737 Patients so Diagnosed, U. S. Naval Med. Bull., 44, 719, 1945. HUNTINGTON, R. W.: Skin Reactions to *Dirofilaria immitis* Extract, U. S. Naval Med. Bull., 44, 707, 1945. MICHAEL, P.: Filariasis: Histopathologic Study, U. S. Naval Med. Bull., 45, 225, 1945.
4. FAIRLEY, N. H.: Serological and Intradermal Tests in Filariasis, Trans. Roy. Soc. Trop. Med. and Hyg., 24, 635, 1931.
5. HODGE, I. G., DENHOFF, E., and VANDER VEER, J. V.: Early Filariasis (*Bancrofti*) in American Soldiers, AM. J. MED. SCI., 210, 207, 1945.
6. IVENGAR, M. O. T.: Studies on the Epidemiology of Filariasis in Travancore, Indian Medical Research Memoir No. 30, Suppl. Series to Indian J. Med. Res., Calcutta, Thacher Spruls, 1931.
7. MANSON: Quoted by Ivengar.
8. O'CONNOR, F. W.: The Aetiology of the Disease Syndrome in Wuchereria Infections, Trans. Roy. Soc. Trop. Med. and Hyg., 26, 13, 1932.
9. ROME, H. P., and FOGEL, R. H.: The Psychosomatic Manifestations of Filariasis, J. Am. Med. Assn., 123, 944, 1943.
10. SAPHIR, W.: Filariasis, J. Am. Med. Assn., 128, 1142, 1945.
11. TALIAFERRO, W. H., and HOFFMAN, W. A.: Skin Reactions to *Dirofilaria immitis* in Persons Infected With *W. bancrofti*, J. Prev. Med., 4, 261, 1930.
12. WARTMAN, W. B.: Lesions of the Lymphatic System in Early Filariasis, Am. J. Trop. Med., 24, 299, 1944.
13. ZELIGS, M. A.: The Psychosomatic Aspects of Filariasis, J. Am. Med. Assn., 128, 1139, 1945.

THE TREATMENT OF BACTERIAL ENDOCARDITIS WITH PENICILLIN*

RESULTS OF 17 CONSECUTIVE UNSELECTED CASES†

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Up to the time that penicillin was introduced little therapeutic advance had been made in the treatment of bacterial endocarditis although considerable work had been done on this disease both as to pathogenesis and therapy.^{8,11,12,13,14,15} The report of Loewe and his associates¹⁷ upon the value of penicillin and heparin opened up new vistas. In our original study it was planned to use heparin with penicillin in half of the cases and penicillin alone in the other half. Our earlier results, presented in a preliminary report,^{19,20} were so promising, however, that it was decided to use penicillin alone in all cases without any anticoagulant. The present report deals with a detailed presentation and follow-up of our first 7 cases previously reported and of 10 additional ones treated since then. All cases were *consecutive* and *unselected*, the only requirement being conclusive clinical evidence of bacterial endocarditis and at least two positive blood cultures in our laboratory.

The method of penicillin administration, the duration of therapy and other similar comments are presented in the discussion which follows the data of the individual cases. The data is presented in the following case reports and is summarized in Table 1.

Case Reports. CASE 1. P. H., a 60 year old female with a history of "heart trouble" since 1939, was admitted to this hospital for terminal care on May 25, 1944 before our study began. A diagnosis of subacute bacterial endocarditis had been made at another institution and the patient had failed to respond to treatment with sulfadiazine and typhoid vaccine. The diagnosis of subacute bacterial endocarditis was substantiated by us before treatment was begun. There were petechiae in the conjunctival sacs, a moderately enlarged heart, aortic and mitral valvular involvement, an enlarged spleen, a temperature of 104° F., and repeated positive blood cultures for *Streptococcus viridans*. The qualitative tests showed the organism to be penicillin sensitive. The patient was given 200,000 units of penicillin by continuous intravenous drip which had to be discontinued after 12 days because of thrombophlebitis and lack of accessible veins. The intramuscular route every 2 or 3 hours was then employed for the remaining 9 days. Five days after completion of the first course, the blood culture revealed a few chains of streptococci which resisted subculture. A second course of 21 days of intermittent intramuscular penicillin was given and the patient then made an uneventful recovery. During treatment, a diastolic murmur over the aortic area became clearly audible for the first time and peripheral signs of aortic insufficiency became apparent. With control

* The penicillin for 15 cases was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council. Penicillin for Case 17 and part of the penicillin for Case 13 was supplied by Commercial Solvents, Inc.

† Aided by the Herbert G. Mayer Fund for Cardiovascular Research. The Cardiovascular Department is supported in part by the Michael Reese Research Foundation.

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TABLE 1.—DATA OF 17 CASES OF SUBACUTE BACTERIAL ENDOCARDITIS TREATED WITH PENICILLIN ALONE

Case	Age and sex	Cardiac diagnosis and duration of infection (weeks)	Previous treatment	Sensitivity units per cc. test broth	Penicillin			Complications	Follow up (months)† and result	Remarks
					Daily usage (units X 1000) and route	No. days therapy	Total units millions			
1. (P. H.)	60 ♀	Rh. A.R. M.D. (16)	Sulfadiazine, typhoid vaccine	Qualitatively sensitive	200 iv drip 25 q.3hr.im 8.3 q.2hr.im 4.2 q.2hr.im 16.6 q.2hr.im (intermittent)	12 8 8 7 21 56	9.3	Thrombophlebitis	Recovered (20)	Mild congestive heart failure. Controlled with digitalis and diuretics.
2. (W. L.)	36 ♂	Rh. A.R. M.D. (5)	None	Qualitatively sensitive	200 iv drip 8.3 q.hr.im 4.3 q.hr.im	8 14 14 36	0.06 5.6	Thrombophlebitis	Recovered (20)	Working. No medication.
3. (R. B.)†	6 ♂	None (3)	Sulfonamides 100,000 units of penicillin	0.04	8.3 q.hr.im 11.1 q.2hr.im	7 14 21	4.2	Urticaria Hay fever	Recovered (18)	Attends school.
4. (W. G.)	51 ♀	Rh. M.S. (10)	None	0.02	8.3 q.hr.im	21	4.2		Recovered (18)	Doing housework. Moderate congestive failure.
5. (O. M.)	19 ♀	Cong. Rh. P.D.A. A.R. (16)	Sulfadiazine (for pneumonia)	0.04	8.3 q.hr.im	42	8.1	Multiple pulmonary infarcts. Infectious mononucleosis	Recovered (16)	Precordial distress.
6. (S. K.)	45 ♂	Rh. A.R. M.D. (13)	4.5 million units of penicillin	0.06	8.3 q.hr.im 200 im drip 300-400 iv drip 300-500 iv drip + q.2hr.im 400 im drip 16.6 q.hr.im 1000 iv and im drip (intermittent)	22 22 26 73 15 158	0.24 0.29 0.60 0.16 57.0	Septic lung infarcts with empyema. Bacteroides septicaemia. Rib resection. Glomerulonephritis.	Relapsed 20 days after last course and died at home shortly thereafter. No autopsy.	Treatment failure.
7. (H. W.)	50 ♀	Rh. M.D. (12)	None	0.04	16.6 q.hr.im 8.3 q.hr.im 4.6 q.hr.im	1 42 3 46	0.24	Essential hypertension. Rheumatoid arthritis.	Recovered (15)	Doing light housework.
8. (M. H.)	35 ♀	Rh. M.D. (26)	None	0.04	8.3 q.hr.im	21	4.2	E. histolytica carrier	Recovered (15)	Fibrillations due to premature systoles.

of the sepsis, mild congestive heart failure appeared which was easily controlled by the usual cardiac régime. The patient was discharged 15 weeks after admission as arrested. She has had no recurrence for 20 months and is gainfully employed as a dressmaker. Her mild heart failure is adequately controlled with digitalis.

The patient was readmitted March 3, 1945 with a pneumococcus (Type 19) infection of the right lower lobe, without any recurrences of the bacterial endocarditis. Several blood cultures were taken at this time which were consistently negative for *Strep. viridans* or other bacteria.

CASE 2. W. L., a 36 year old male with a rheumatic history since childhood but with little cardiac disability was admitted on May 4, 1944, with chills, fever, malaise and generalized weakness of 2 weeks duration following an upper respiratory infection. Examination showed the presence of mitral and aortic valvular involvement. Four blood cultures were positive for *Strep. viridans*. Qualitative tests showed the organism to be penicillin sensitive. There was consolidation in the right lower lobe, believed to be due to pulmonary infarction. The patient was given 200,000 units of penicillin by continuous intravenous drip for 8 days. The temperature which had fallen to normal levels at the onset of treatment rose again during treatment and blood cultures became positive. The route of therapy was changed and 8300 units were given intramuscularly every hour on the hour day and night for 2 weeks; then 4300 units were given per dose in the same manner for an additional 2 weeks. The temperature promptly dropped and the patient made an uneventful recovery. He was discharged from the hospital June 30, 1944 and has been back at his former occupation. He has been asymptomatic and has had no recurrence for 20 months.

CASE 3. R. B., a 6 year old male, with no previous history of, or findings indicating, congenital or rheumatic heart disease, but with a history of hay fever and allergic food idiosyncrasies developed a rise in temperature to 106° F. 1 day after tonsillectomy. He was given sulfanilamide and sulfadiazine and 100,000 units of penicillin at another institution after a blood culture containing a hemolytic streptococcus was obtained. The response was not satisfactory. On admission, on Aug. 10, 1944, the temperature was

106° F. The child was dehydrated and drowsy. Two blood cultures were positive for *Strep. hemolyticus*, sensitivity 0.04 Oxford units of penicillin. A harsh, systolic murmur at the apex was present with transmission towards the axilla. The family physician stated that no murmur was present previous to the present illness. During treatment, the murmur became more blowing and higher pitched. The heart was of normal size on Roentgen ray and fluoroscopy. The urine was normal on microscopic examination and sterile on culture. The tonsillar fossæ were healed. The child was given 8300 units of penicillin intramuscularly every hour day and night for 1 week. Because of the high blood serum levels obtained and because of the immediate rapid favorable response, he was then given 11,100 units intramuscularly every 2 hours for the next 14 days. The child developed a generalized urticaria on the second day of treatment, which responded to symptomatic treatment. The blood cultures soon became sterile. The patient was sent home symptom free on the 38th day. He has returned to school, has had no recurrence for 18 months and is carrying on normal activity. A residual soft systolic blowing murmur at the apex has disappeared.

CASE 4. W. G., a 51 year old woman, with a vague history of rheumatic fever in 1906, was admitted on Aug. 11, 1944 with fever and weakness of 10 weeks duration. On May 15, 1944, the patient had a tooth extracted and was given sulfathiazole prophylactically. On June 3, a second abscessed tooth was extracted but no sulfonamide was given because the patient was nauseated after the previous sulfathiazole administration. Two days following the tooth extraction the patient became febrile. Three blood cultures were positive for *Strep. viridans*, sensitivity 0.02 Oxford units. On examination, the patient had a café-au-lait color, a temperature of 104° F., a palpable, soft and tender spleen, an enlarged heart with an apical presystolic murmur. Starting on the 9th hospital day, 8300 units of penicillin were given intramuscularly every hour day and night for 21 days. The response was dramatic and complete. The patient was sent home on the 38th day. At present, she is doing light housework with only slight cardiac disability. She has had no recurrence for 18 months.

CASE 5. O. M., a 19 year old girl with a past history of congenital heart disease and congenital syphilis. She had received intensive bismuth and arsenical therapy. One week following extraction of an abscessed tooth, she began to have chills and fever. The patient was treated at another institution with sulfadiazine with no response. On admission on Aug. 23, 1944, the girl was acutely ill, with pain in the right lower chest. On examination, there was consolidation of the right lower lobe, a "machinery-like" murmur heard best in the pulmonic area and a questionable early diastolic high pitched murmur heard best at Erb's point. Three blood cultures were positive for *Strep.*

in the dilution of 1 to 32. Intramuscular penicillin therapy was continued for 6 weeks. It is interesting that the blood cultures remained sterile for *Strep. viridans* during the concurrent infectious mononucleosis. The diastolic murmur at the base became more audible and a diagnosis of aortic insufficiency was made. During treatment, several abscessed teeth were removed* and the sockets packed with penicillin (5000 Oxford units per cc.) soaked sponges. Culture of the sockets before packing revealed *Strep. viridans* predominating. The patient was discharged on the 53rd day after admission. At present the patient experiences mild

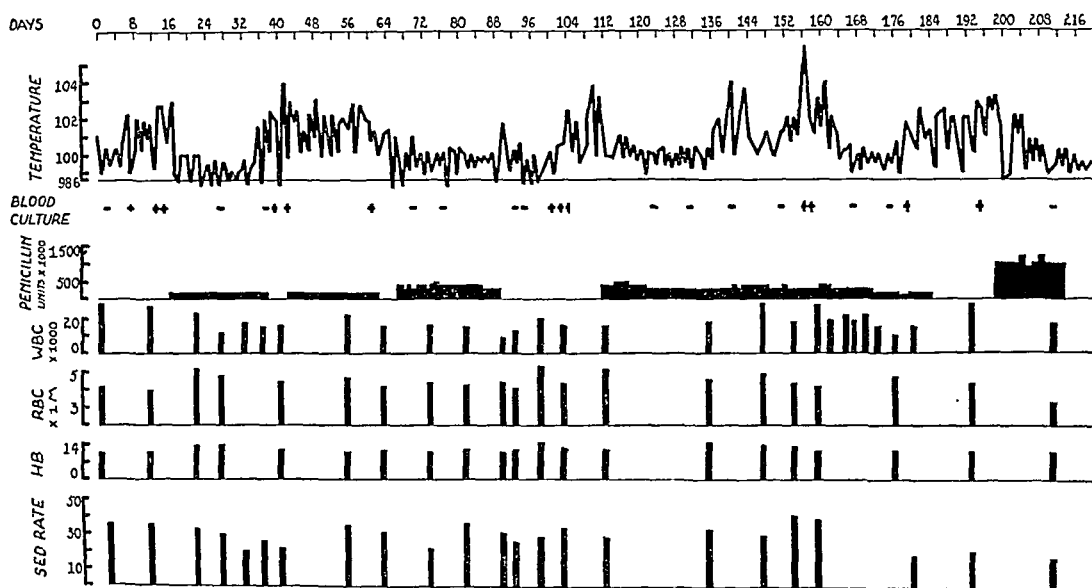


FIG. 1.—Course during hospital stay of Case 6. This illustrates a treatment failure due to organism resistance, embolic complications and inadequate penicillin dosage.

viridans, the sensitivity was 0.04 Oxford units. On the 3rd hospital day, the patient was given 8300 units of penicillin intramuscularly every hour day and night. There was a dramatic response in temperature and "clinical well-being" within 48 hours. At the end of 2 weeks, at which time the lung had almost completely resolved, the patient developed a pharyngitis with cervical lymphadenopathy and the temperature rose to as high as 102° F. over the next 6 days. Several blood smears showed mononuclear cells characteristic of infectious mononucleosis. The heterophil agglutination test was positive

dyspnea on moderate exertion as well as precordial distress, but has had no recurrence for 16 months. Ligation of the ductus is not contemplated because of the concomitant aortic valvular defect.

CASE 6. (Fig. 1.) S. K., a 45 year old man, was admitted on Aug. 24, 1944, from another institution, where a diagnosis of acute endocarditis was made because of 4 positive blood cultures for *Strep. hemolyticus*, the presence of aortic and mitral valvular disease, and embolic phenomena. In May, 1944, he had had several teeth pulled and soon thereafter he had weakness, malaise,

* The oral surgery on this and our other patients was performed by Dr. M. Falstein.

and fever. He had previously received a total of 4.5 million units of penicillin by the intramuscular route, administered every 3 to 4 hours. There was no previous history of rheumatic infection or cardiac disability. Physical examination showed evidence of moderate weight loss, aortic and mitral valvular involvement, embolic phenomena, a palpable spleen and slight clubbing of the fingers. The first blood culture was negative, but three taken subsequently were positive for *Strep. viridans*, sensitivity was 0.06 Oxford units. On Sept. 9th, the patient was started on 200,000 units of penicillin per day at the usual concentration, 8300 units intramuscularly every hour during the 24 hour period. This was continued for 3 weeks. The initial

units daily by continuous intravenous drip. The temperature responded slightly and embolic phenomena were almost constant although the blood stream was sterilized. However, 6 days after this course of therapy was ended the blood culture was again positive for *Strep. viridans*, which still showed the same sensitivity, viz., 0.06 Oxford units. A fourth uninterrupted course of therapy of 73 days was begun on Dec. 12th, employing from 300,000 to 500,000 units daily. This was given by continuous intravenous drip augmented by intramuscular injections every hour for several days; then by alternating continuous intramuscular injections. Renal and splenic emboli were common. Renal studies showed a fixed specific gravity and

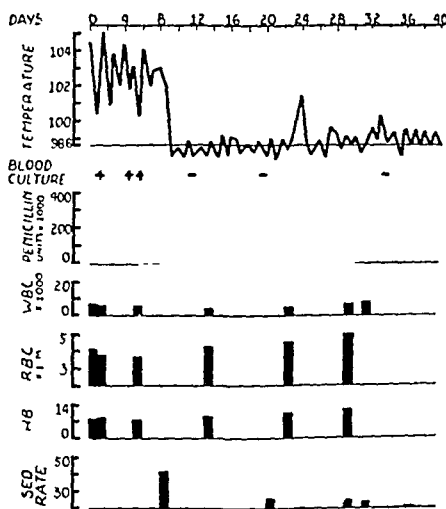


FIG. 2.—Course during hospital stay of Case 8. This illustrates the rapid and sustained response which many of the patients showed. The temperature rise on the 25th day was due to a transfusion reaction.

response was good. The blood level of penicillin was 0.24 units at the end of 1 hour. On the last day of the 3 week treatment, his temperature spiked and the blood culture was positive. The patient was started on a second course of therapy on Oct. 5th, at the same total daily dosage of penicillin, but by continuous intramuscular drip. The temperature did not reach normal levels at any time during this course, and he began to vomit, necessitating parenteral nutritive therapy for 1 week. There were numerous petechiae and the vomiting was believed to be of central origin. The blood culture was positive during this course of treatment. A third period of treatment of 26 days was begun on Oct. 30th, using 300,000 to 400,000

a urea clearance 30% of normal. The blood chemistry was at the upper limits of normal as were circulation time studies. Several infected teeth were removed. The sockets on culture showed *Strep. viridans*, and they were packed with penicillin. On Dec. 26th, the patient's temperature spiked to 106° F. and there were signs of fluid in the right chest. Blood culture was positive for *Strep. viridans* and Gram negative pleomorphic anaerobic non-spore bearing bacillus which morphologically and culturally resembled *Bacteroides funduliformis*.¹⁰ Chest tap revealed foul-smelling pus with the presence of the two organisms described. Thoracotomy and rib resection was done by Dr. R. Bettman. Large quantities of pus in locu-

lated spaces in the pleural cavity were removed and the pleural space drained. The chest cavity was irrigated daily with surface active azochloramine followed by instillation of 30,000 to 50,000 units of penicillin. Because of the concomitant bacteroides infection, which could not be inhibited by penicillin *in vitro*, a total of 88 gm. of sulfanilamide and sulfadiazine were given over a period of 2 weeks postoperatively. The sulfadiazine blood level was 9.5 mg. %. Several transfusions and amino acid infusions were administered. Six days before therapy was stopped, the patient had a positive blood

The temperature gradually fell to normal and the blood stream remained temporarily sterilized after stoppage of therapy. The thoracotomy wound was now practically healed. After a hospital stay of 221 days and treatment for 158 days, using a total of 57 million units of penicillin, this patient was sent home. Unfortunately, 3 weeks after treatment was stopped, his blood culture again became positive. Shortly thereafter the patient died in his sleep while at home. Autopsy permission was not obtained.

CASE 7. H. W., a 50 year old woman with a history of essential hypertension of 10 years

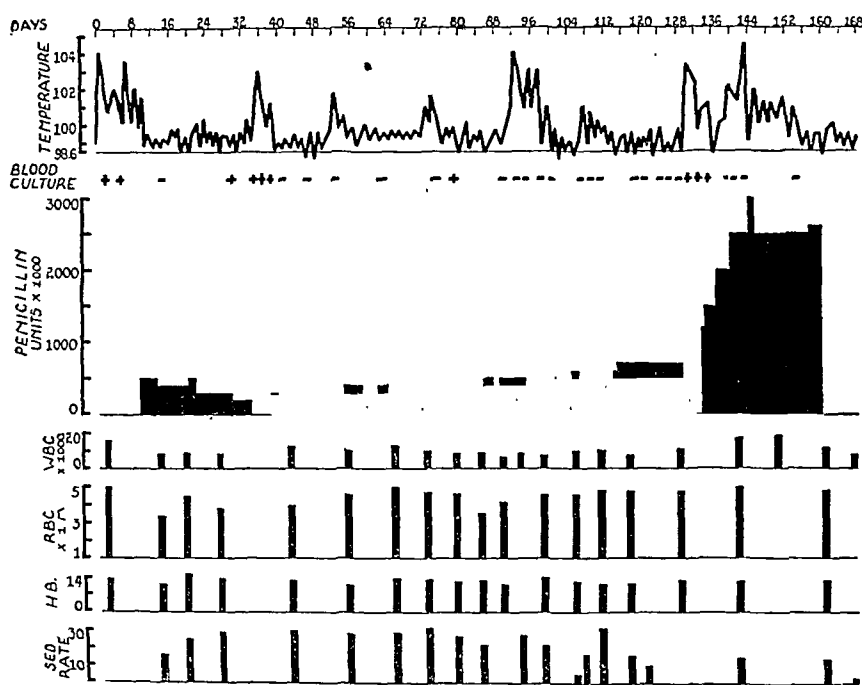


FIG. 3.—Course during hospital stay of Case 13. This illustrates the successful outcome of a resistant case when the penicillin dosage was increased. The temperature rises are due to the recurrent bacteremia when penicillin was stopped or to multiple pulmonary infarcts during the treatment period.

culture for *Strep. viridans*. Because of the recurrence of bacteremia when therapy was stopped, the rising temperature, and the ever present leukocytosis after this extensive treatment, we thought it was useless to continue treatment and called this patient a treatment failure. When penicillin became more readily available, a fifth course of treatment was nevertheless begun, using 1 million units daily by the continuous intramuscular drip for 15 days, supplemented by two daily interrupted intramuscular injections of 100,000 units given 20 minutes apart, during the last 10 days of therapy.

duration with no renal impairment and painful swellings of the interphalangeal and metacarpophalangeal joints, was admitted on Sept. 31, 1944 with the generalized complaints of weakness and anorexia of 3 months duration, chills and fever, and painful swelling of the dorsum of right foot of 4 days duration. Examination showed several conjunctival petechiae, a typical Osler node on the dorsum of the right foot, enlarged heart with mitral presystolic murmur and other evidence pointing to mitral involvement. Several blood cultures were positive for *Strep. viridans*, the sensitivity was 0.04 Oxford

units. The patient received the now established 3 week course of penicillin, 8300 units intramuscularly every hour day and night. The temperature did not return to normal, during therapy, although blood cultures were sterile. A second similar course of penicillin was therefore given and the response to this was good, although the patient continued to have typical Osler nodes on the thenar and hypothenar eminences of both hands which gradually disappeared. The patient was discharged 75 days after admission. The sedimentation rate did not return to normal until several weeks after the patient was discharged. She is now doing light housework and has had no recurrences for 15 months.

drop in temperature and clinical "well-being" occurred within 36 hours. On the 25th treatment day, the temperature rose to 101.4° F. because of a transfusion reaction. Stools were positive for *Endamæba histolytica* and a course of carbarsone was given. Subsequently to this stool study has been negative. Prophylactic extraction of several teeth was performed during the penicillin treatment period without untoward effects. The patient was discharged on the 40th hospital day asymptomatic. This patient showed a rapid and complete response to treatment—the café-au-lait color disappeared, the hemoglobin (which was 7 gm.% on admission) had returned to normal on discharge, the



FIG. 4.—Case 15. Close-up view of aortic valve and anterior leaflet of the mitral valve showing friable vegetations on the right and non-coronary cusp of aortic valve. Vegetations on chordæ tendineæ showed almost complete healing by organization and regrowth of endothelium. No bacteria were present. Vegetations on the left coronary cusp showed healing with no colonies of bacteria present. Note perforation of anterior mitral leaflet.

CASE 8. (Fig. 2.) M. H., a 35 year old woman with a history of heart disease since the age of 16, was admitted on Oct. 12, 1944 with the complaints of fever and weight loss of 6 months duration. Examination revealed a typical café-au-lait color, petechiæ in the left conjunctival sac, marked splenic enlargement, and enlarged heart with evidence of a mitral stenosis, and a temperature 104° F. The blood cultures were repeatedly positive for *Strep. viridans*, the sensitivity was 0.04 Oxford units. The patient was given 8300 units of penicillin intramuscularly every hour for 21 days. A precipitous

sepsis had rapidly disappeared, and her personality quickly changed from complete negativism to coöperativeness and sociability. Since discharge, she has been doing housework and has had no recurrence for 15 months.

CASE 9. E. T., a 36 year old male Negro with a history of syphilis 15 years before, for which he had received irregular treatment for about 2 years, was admitted on Oct. 25, 1944, with the complaints of painful finger tips, epistaxis, headaches, migratory joint pains, chills, and fever of 9 weeks duration. Examination showed several pete-

chiae in the conjunctival sacs, Osler nodes on the finger tips, markedly enlarged heart with aortic insufficiency and mitral valvular involvement. The left knee and right ankle were swollen, hot and tender, temperature 102° F. The electrocardiogram showed prolongation of the P-R interval to 0.30 second. The blood cultures were positive for *Strep. viridans*, the sensitivity was 0.04 Oxford units. He received 8300 units of penicillin intramuscularly every hour day and night for 10 days during which time the chills and fever continued, petechiae were numerous, and subungual splinter hemorrhages appeared. Continuous intramuscular and intra-

duction time returned to normal within a month. The Wassermann, Kahn and Eagle reactions, which were positive before treatment did not change qualitatively or quantitatively after treatment. Near completion of therapy, signs of cardiac insufficiency developed and paroxysmal dyspnea was common. Digitalization did not improve his symptoms but periodic mercurial diuretics were helpful. He was discharged on the 94th hospital day.

Two weeks following discharge, and 9 weeks after penicillin was stopped, he complained of sudden pain in his left foot. Examination showed absent pulsations in the



FIG. 5.—Case 14. Heart showing ulceration and fragmentation of bicuspid aortic valve. Vegetations revealed *Strep. viridans* on culture.

venous drips were then started employing 200,000 to 400,000 units of penicillin daily. Embolic phenomena were almost continuous. Several abscessed teeth were removed and the routine of packing of the sockets with penicillin employed. No untoward effects were observed. During the last 5 days of treatment, 500,000 units daily were used by the hourly intramuscular route. The temperature gradually fell to normal. Two days before penicillin was stopped because of the then unavailable supply, he had a new crop of petechiae. He received a total of 16.8 million units of penicillin during 46 continuous treatment days. The prolonged A-V con-

left dorsalis pedis and posterior tibial arteries, swelling and coldness of the left foot. Repeated blood cultures were sterile. On vasodilators and symptomatic treatment, pulsations returned, edema subsided, and the patient made an uneventful recovery. This episode was interpreted as a sterile embolization to the posterior tibial artery. He later developed a peculiar musical diastolic murmur over Erb's point. Although this case was complicated by positive Wassermann and Kahn tests, and posttreatment sterile embolization, the patient made a good recovery from his subacute bacterial endocarditis and there had been no evidence of

its recurrence until the patient's death, 8 months later. The patient, however, developed moderate congestive failure, and required digitalis, mercurials and restriction of activities for its control.

He was readmitted to the hospital on June 18, 1945, 6 months after he had been discharged following successful penicillin therapy) because of progressively increasing congestive heart failure. All attempts to control his heart failure were unsuccessful. He died on Aug. 26, 1945 (8 months after penicillin therapy had been successfully used). Blood cultures during this admission were repeatedly negative.

grayish streaks throughout. The wall of the right ventricle measures 0.5 cm., that of the left ventricle 1.4 cm. There is a red slightly attached thrombus at the appendage of the right auricle. Several yellowish gray, moderately firm thrombi are attached to the endocardium of the right ventricle. They measure up to 2 cm. in greatest dimension. The endocardium of the left auricle, just above the mitral valve, shows several firm, grayish, smooth projections and whitish striae. The tricuspid and pulmonic valves show no gross changes. The severely disfigured aortic valve shows a thickening and rolling of the free margins with a hyaline plaque (6 mm. in diameter) projecting from the intima of the

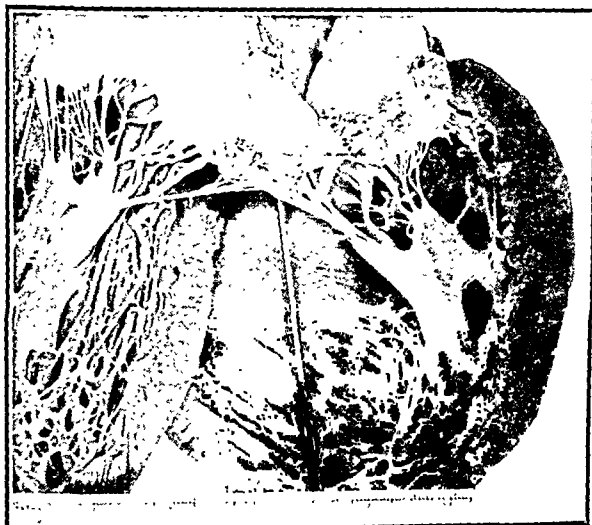


FIG. 6.—Case 14. Heart showing aneurysm formation with perforation of the anterior mitral leaflet. There are many vegetations on both leaflets of the thickened scarred valve.

AUTOPSY revealed: healed subacute bacterial endocarditis of the mitral and aortic valves with a perforated aneurysm of the mitral valve, aortic valvulitis, syphilitic aortitis involving the aortic valve and encroaching on the mouth of the right coronary artery, pulmonary embolus with infarction and chronic passive hyperemia. There were no fresh vegetations present. The important gross and histological findings are illustrated in Figures 7 to 14.

The following pertinent data are from the pathologist's report:

Gross Description of Heart. The heart is moderately enlarged (450 gm.) and is moderately dilated in all chambers. The pericardium is smooth and glistening. The myocardium is firm, brown, and shows a few

aorta and separating the commissures, between the right and posterior cusps. It had also encroached upon the mouth of the right coronary artery. The plaque measures about 6 mm. in diameter. The posterior cusp is markedly shortened, the noduli Arantii are displaced towards the commissure, and it exhibits a perforation 4 mm. in diameter. The aortic ring is distinctly dilated, measuring 9 cm. in circumference.

The aortic leaflet of the mitral valve contains a broad aneurysmal outpouching (2×3 cm.), with a 3 mm. perforation (see Fig. 6). The auricular surface of the lesion and of the remainder of the valve is smooth and glistening; the ventricular surface is roughened with the outpouchings separated by slender bands of scar tissue. However, no

recent vegetations are present. There is no obvious thickening of the line of contact of the valve apart from the aneurysm. One chorda tendineum of the aortic leaflet is moderately thickened; the rest are delicate. The roughening due to the scar tissue extends to the aortic valve on the endocardium of the left ventricle.

The mitral valve measures 8 cm., the pulmonic 7 cm., and the tricuspid 13 cm. in circumference. The mural endocardium of the interventricular septum of the left ventricle, and especially just beneath the aortic valve, discloses a diffuse, whitish thickening. In one region, close to the attachment of the aortic leaf of the mitral valve, there is a small, roundish, whitish defect,

jacent areas show moderate hyalinization. In other fields there is a rich infiltration of lymphocytes and monocytes with newly formed blood vessels. At the most distal part of the aortic leaf of the mitral valve small foci of necrosis are encountered, surrounded by monocytes and lymphocytes. Other sections show, at the periphery of this leaflet, an obvious new formation of lining endothelial cells with hyperchromatic nuclei. Occasionally some of the monocytes are heaped up and project over the surface. In other sections again, attached to the surface of the valve, there are a few projections consisting of young connective tissue cells with a few scattered lymphocytes. Occasionally, a few areas of dark bluish stained, granular



FIG. 7.—Case 9. Aortic valve and aortic leaf of the mitral valve. Note the narrowing of the mouth of the right coronary artery, the hyalinized plaque with horizontal wrinkling of the aorta, the separation of the commissure and the rolling and thickening of the aortic cusps. Also note the saccular cavity in the aortic leaf of the mitral valve.

3 mm. in diameter, which leads into a shallow, smooth-walled cavity. Some of the thickened areas have produced pockets, their opening directed either towards the aortic valve or towards the apex of the heart.

The aorta has lost some elasticity. In its ascending portion, close to the sinus of Valsalva, the endocardium discloses a number of reddish plaques and horizontally placed wrinkles with red bases, also areas of hyalinization and foci of fatty degeneration. The mouth of the right coronary artery is distinctly narrowed; that of the left is patent; they show only a moderate arteriosclerosis.

MICROSCOPIC EXAMINATION. *Mitral Valve.* In some fields there is a marked thinning of the substance of the valve with some new fibroblasts and infiltrated lymphocytes. Ad-

material can be made out. Special stains show this to consist of calcium and intermingled Gram positive cocci.

Aortic Valve. The free margins of the aortic cusp show a new partly hyalinized connective tissue containing minute elastic lamellæ, a moderate infiltration of lymphocytes, and insignificant foci of necrosis. The midportion of the cusp is somewhat thicker than normal and its ventricular surface contains new connective tissue cells and fibers with a number of lymphocytes and rare neutrophils. Close to the base of the valve there are occasionally found small projections consisting of many spindle-shaped nuclei, surrounded by one layer of flat epithelial cells. The free margins of the cusps disclose centers of necrosis surrounded

by connective tissue fibers with a large number of elastic lamellæ. The base of the sinus of Valsalva shows a new formation of blood vessels, some of which are surrounded by lymphocytes.

Aorta. There is, in many fields, an interruption of the elastic lamellæ of the media. The adventitia in corresponding areas shows a perivascular infiltration of lymphocytes of varying degrees associated with a thickening of the walls of the vasa vasorum and diffuse fibrosis.

lamellæ of the media, the marked thickening of the adventitia with perivascular round cell infiltrations, are characteristic. The older inflammation in the cusps (new formed connective tissue with scattered lymphocytes and a few monocytes) is obviously not associated with the syphilitic process. The organized and healing vegetations are lined by regenerated endothelial cells. It is perhaps significant of the type of the inflammatory changes that the adjacent portion of the septal endocardium shows similar



FIG. 8.—Case 9. Mitral valve (auricular aspect). Note the bulging aneurysm and the perforation.

Sections taken from the uppermost portion of the interventricular septum, just beneath the aortic valve, shows the endocardium covered by much old granulation tissue with many spindle-shaped nuclei. Very rarely an occasional neutrophil is encountered.

Myocardium. Within the myocardium there are many fields where the muscle fibers are interrupted by minute healed infarcts (old scar tissue containing a number of blood vessels). There are also small areas of fibrosis, especially in perivascular regions. Here and there small foci of lymphocytes, monocytes, and plasma cells are present in the perivascular spaces. Nowhere is there any evidence of Aschoff bodies.

Summary of the Heart Findings. Significant changes were found in the aortic and mitral valves. The basic lesion of the aortic valve is obviously syphilitic aortitis which had extended into the sinus of Valsalva. Grossly, the separation of the commissures, the presence of a hyaline plaque at the region of the commissures and the narrowing of the mouth of the coronary artery, are pathognomonic. Histologically, the interruption of the elastic

changes. This suggests that the acute inflammatory lesions had extended from the aortic valve to the mural endocardium—a common finding in acute and subacute bacterial endocarditis.

The mitral valve lesions are unusual. Outstanding were the thinning and bulging of the aortic leaf of the mitral valve with perforation, the bulge directed towards the auricle. The cause for the bulge, as clearly seen in the histologic section, is an older valvulitis which had caused the thinning, *i. e.*, a mycotic aneurysm. Evidence is also present of a diffuse valvulitis in the healing and healed stage with many connective tissue cells, a few lymphocytes and only very few neutrophils. In one region, close to the free margin foci of necrosis with a few bacteria (or stained precipitate) are still encountered. It is important that these areas were completely surrounded by connective tissue cells and fibers, and that the free surfaces of the leaf were covered by apparently regenerated endothelial lining cells. No cultures were made of these areas.

The myocardium showed multiple minute

infarcts with many foci of fibrosis and rare small areas of localized subacute and chronic myocarditis. Nowhere in the sections was anything found that could be interpreted as remnants of Aschoff bodies.

Thus, it is clear that this is a case of a syphilitic aortitis and aortic valvulitis with insufficiency. It is also evident that an acute or subacute bacterial endocarditis had been superimposed upon the syphilitic process. This was definitely in the healing and healed stage. Because the endocarditis was superimposed upon an older (syphilitic) lesion, because it had extended to the adjacent mural endocardium and endocardium of the mitral valve, and because throughout the

sound from cycle to cycle with jugular pulsations at times other than that of the first heart sound. The pulse varied from 50 to 64, although the temperature was 103° F. The electrocardiogram showed complete A-V heart block. Blood cultures were positive for *Strep. viridans*, the sensitivity was 0.03 Oxford units. The patient was given 8300 units of penicillin intramuscularly every hour day and night. Clinical improvement was rapid and maintained. Laboratory studies corroborated the clinical impression. Treatment was stopped on the 18th day and the patient was discharged on the 33rd hospital day, asymptomatic. She is back at

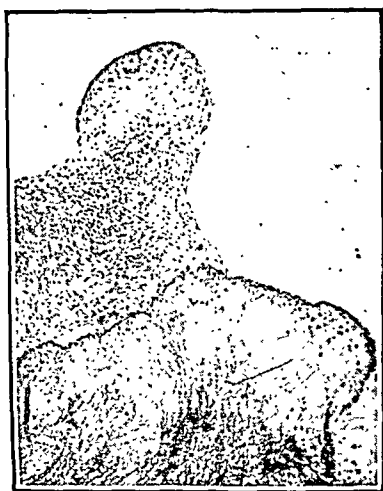


FIG. 9.—Case 9. Healing vegetation, aortic valve. Note the regenerated endothelial lining cells. Orcein preparation; $\times 45$.



FIG. 10.—Case 9. Mitral valve. Note the rich granulation tissue. Iron-hematoxylin-eosin preparation; $\times 125$.

myocardium multiple small infarcts were encountered, it is safe to assume that the endocarditis must be classified, from the morphologic standpoint alone, as subacute bacterial endocarditis. The patient died as a result of myocardial failure. This is a complication of arrested subacute endocarditis.

CASE 10. A. R., a 22 year old woman with a history of congenital heart disease and "slow pulse" was admitted on Nov. 7, 1944 because of unexplained fever of 6 weeks duration. On examination, there was a subungual splinter hemorrhage, an enlarged heart, a long, rough systolic murmur present over the entire precordium, parasternally, with varying intensity of the first heart

her former occupation and has had no recurrence for 14 months.

CASE 11. E. B., a 22 year old woman, followed since birth at another hospital with a diagnosis of patent interventricular septum, was admitted Nov. 20, 1944, with fever, blood streaked sputum and generalized weakness, of 4 weeks duration. She had been treated at home with sulfadiazine with no improvement. Examination revealed an enlarged heart, a systolic thrill, a loud rough systolic murmur (best heard in the 5th intercostal space parasternally), and consolidation in the right lower lobe. The temperature was 102.8° F. Blood cultures were positive for *Strep. viridans*, the sensitivity was 0.03 Oxford units. The patient was given 8300

units of penicillin every hour day and night for 21 days. Response was good, but there were temperature rises to as high as 100.6° F. at times. Several abscessed teeth were removed and the usual penicillin routine followed. During and after the treatment, the patient had unexplained paroxysms of hacking, non-productive coughing spells lasting 1 to 2 hours, causing exhaustion. Sodium amytal and morphine had to be used to depress the patient. Bronchoscopy (Dr. S. Salinger) showed marked congestion and edema of the right main bronchus; the left was normal. With symptomatic treatment and frequent psychiatric interviews (Dr. M. Gitelson), the coughing spells lessened and ceased. The patient was discharged on the 63rd hospital day. After being back at work for 6 months, she developed several petechiæ.

frequent epistaxes, of 4 months duration. Examination revealed a temperature of 102.2° F., an enlarged heart, a systolic thrill and a loud rough systolic murmur heard best at the 3rd intercostal space parasternally, a markedly enlarged spleen, numerous petechiæ over the lower abdomen and legs, and early clubbing of the fingers. Blood cultures were positive for *Strep. viridans*, the sensitivity was 0.03 Oxford units. He was treated for 25 days day and night with the hourly intramuscular injection of penicillin varying from 100,000 to 300,000 units daily. Defervescence and clinical improvement were

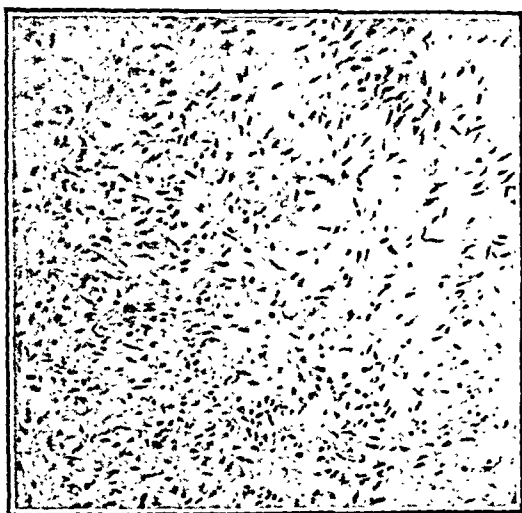


FIG. 11.—Case 9. Early scar tissue. Mitral valve. Iron-hematoxylin-eosin preparation; $\times 125$.

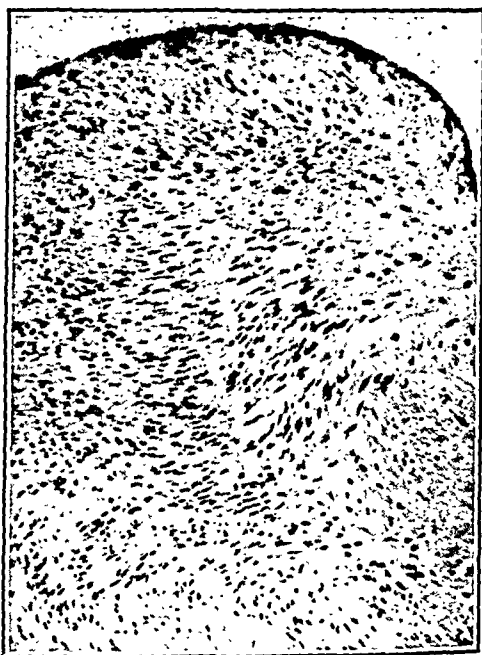


FIG. 12.—Case 9. Aortic valve. Note the cellular scar tissue covered by regenerated endothelial lining cells. Orcein preparation; $\times 125$.

She was readmitted to the hospital where she ran an evening temperature of 99.6° F. Repeated blood cultures have been negative. After several weeks observation she was discharged. Since then she has had occasional petechiæ, but blood cultures are negative. No fever or evidences of heart impairment have been manifest. Thus it appears that the patient has had no recurrences for 13 months.

CASE 12. R. S., a 12 year old boy with a history of "heart murmur" since the age of 2, was admitted on Nov. 20, 1944 with weakness, weight loss, fever, joint pains and

prompt. There were slight temperature rises following extraction of several infected teeth during the course of therapy. The stay in the hospital otherwise was uneventful. The patient was discharged on the 46th hospital day. The boy is back at school, is asymptomatic and has had no recurrence for 13 months.

CASE 13. (Fig. 3.) S. H., a 38 year old man with a history of congenital heart disease since birth was admitted on Nov. 22, 1944 from another institution where a diagnosis of subacute bacterial endocarditis was made and a total of 5 million units of penicillin given without response. His complaints

were fever, headache and "tightness of the forehead" and generalized malaise of 4 months duration. The diagnosis was confirmed bacteriologically and clinically. On examination, the heart was not enlarged. There was a systolic thrill and loud harsh murmur best heard in the 3rd intercostal space para- and midsternally. There was no sign of peripheral embolization nor has any appeared as yet. His stools carried *Ascarsis lumbricoides*; and flagellates were found in the urine; both were successfully treated. The blood cultures were positive for *Strep. viridans*, sensitivity was 0.03 Oxford units. Because of the previous unsuccessful treatment, he was given 300,000 to 500,000 units daily by hourly intramuscular injections day and night. Defervescence was immediate but headaches persisted. One day after completion of the first course of penicillin,

negative. A neurologic examination was normal. As soon as therapy was again stopped, blood cultures became positive. The organism had not changed its sensitivity. A third course of treatment employing 1.2 to 3 million units daily by continuous intramuscular and intravenous drip was successful. During this last course, he received for 72 hours penicillin dissolved in 3000 cc. of 6% para-aminohippuric acid.² His blood penicillin level under this combination rose to 5 Oxford units per cc. This patient has received over 112 million units of penicillin.

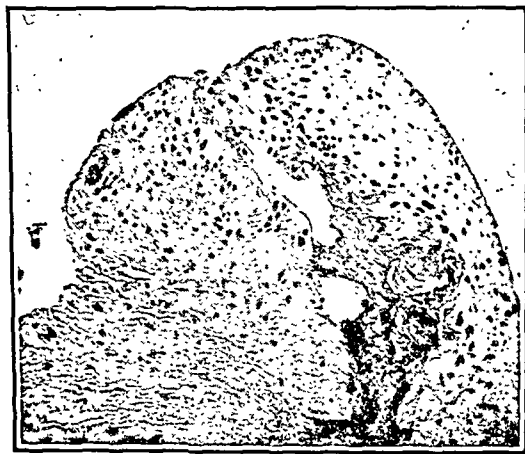


FIG. 13.—Case 9. Mitral valve. Note the area of necrosis. Iron-hematoxylin-eosin preparation; $\times 125$.

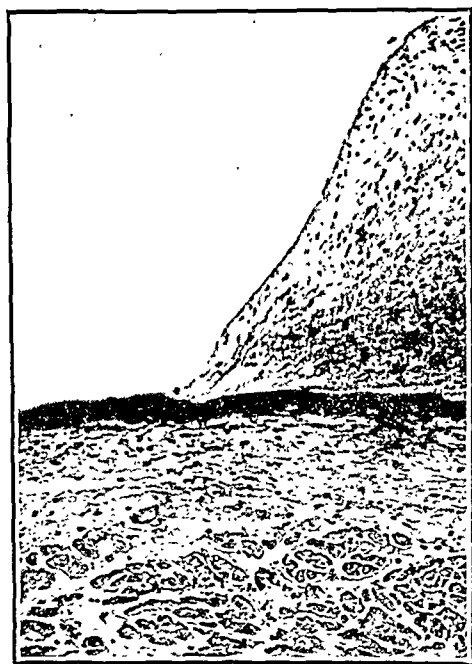


FIG. 14.—Case 9. Mural endocardium. Note the plaque indicating healing mural endocarditis. Orcein preparation; $\times 125$.

the temperature rose and the blood cultures became positive. He was then given a prolonged course of treatment of 92 continuous days of interrupted intramuscular injections using at times concomitantly intravenous drip. The lowest level of penicillin maintained in the blood was 0.16, and often it was 0.50 to 0.74 units per cc. In addition, "booster doses" as recommended by Baehr¹ were given for 15 days. During treatment, there were many episodes of pulmonary embolization. His headaches would disappear for several days and then would reappear. Examination chemically and bacteriologically of the spinal fluid was entirely

He is back at work and has had no recurrences for 10 months.

CASE 14. R. M., a 40 year old man, with a past history of "heart disease" since the age of 20, was admitted on Dec. 10, 1944, from another institution with a diagnosis of subacute bacterial endocarditis of 11 months duration. He had been treated with sulfa-pyridine, sulfadiazine, and 500,000 units of penicillin before admission. On examination, the patient was obviously very far advanced in his illness. He was dyspneic, orthopneic, had a café-au-lait color with many petechiæ on the soft palate and in both conjunctival sacs, and marked clubbing of the fingers.

The heart was markedly enlarged and there was evidence of aortic and mitral valvular involvement, with gallop rhythm. There was marked edema of the lower half of the body, bilateral pleural effusion and ascites with hepatosplenomegaly. The muscles were obviously wasted and atrophic. The blood cultures were positive for *Strep. viridans*, the sensitivity was 0.08 Oxford units. The temperature was 103° F.; hemoglobin 8 gm., 2.8 million red blood cells. The total blood protein was 4.2 gm. % (2.2 gm. albumin and 2 gm. of globulin). The venous pressure was 20 cm. of water. The circulation time was prolonged. Because of the wasted gluteal muscles and edema, he was given hourly injections of penicillin (12,500 units per dose) day and night into the deltoid muscles. In addition, frequent small whole blood transfusions, digitalis, mercurials, and a high protein (150 gm.) salt free diet were given. The temperature never fell to normal under treatment. By the 15th hospital day the blood albumin level had increased 0.8 gm. %. However, the patient became progressively worse and died in congestive heart failure after receiving a total of 3.9 million units of penicillin for 12 days. The valve lesions are shown in Figures 5 and 6.

The salient autopsy findings (Dr. O. Saphir) were:

1. Subacute bacterial endocarditis (*Strep. viridans*) of the mitral and aortic valves with ulcerations of the aortic cusps and mycotic erosive aneurysm of the mitral valve.

2. Multiple organizing and organized myocardial infarcts (embolic in origin).

3. Marked chronic passive hyperemia of lungs, liver and kidneys.

CASE 15. A. B., a 27 year old man, with a past history negative for rheumatic fever was transferred to this hospital on Dec. 28, 1944 from another institution with a diagnosis of subacute bacterial endocarditis. He had been ill for 10 months and had been at several hospitals where he had received various sulfonamides and a total of 3 million units of penicillin irregularly administered. The diagnosis was substantiated clinically and bacteriologically. On examination there were obvious peripheral signs of aortic insufficiency. The heart was markedly enlarged. There was a left hydrothorax, several petechiæ in the right conjunctival sac, and clubbing of the fingers. Blood cultures were positive for *Strep. viridans*, the sensitivity was 0.02 Oxford units. He was given 300,000

to 400,000 units of penicillin by the hourly interrupted or by the continuous intramuscular drip. The temperature never returned to normal and the patient continued to have splenic and renal infarcts. On the 35th day of treatment after he had received 11.4 million units of penicillin, he suddenly became aphasic, lapsed into a coma and died.

The salient autopsy findings (Dr. O. Saphir) were:

1. Subacute bacterial endocarditis of the aortic (*Strep. viridans*) and mitral valves (Fig. 4).

2. Ruptured mycotic aneurysm of the mitral valve.

3. Embolus in the left middle cerebral artery.

4. Hemorrhage in the left cerebral hemisphere.

5. Large septic infarcts of the spleen.

6. Mycotic aneurysm of the splenic artery.

CASE 16. E. R., a 21 year old woman had a history of rheumatic pancarditis with congestive failure at the age of 8. Subsequently, she had slight to moderate cardiac disability. She was admitted on Jan. 1, 1945, with fever, painful finger tips of 3 weeks duration, and amenorrhea of 12 weeks duration. Physical examination revealed murmurs of aortic insufficiency and mitral stenosis, Osler nodes on the terminal phalanx of the left ring finger and right first toe and an irregularly enlarged uterus to the size of a 3 months gestation. Friedman test and pregnandiol test for pregnancy were positive. Three successive blood cultures were positive for *Strep. viridans*, the sensitivity was 0.015 Oxford units. She was given 8300 to 16,600 units of penicillin every hour day and night for 56 days intramuscularly. The temperature response was dramatic and the blood stream was easily sterilized. It was felt that continuation of pregnancy was not justifiable because of the previous history of congestive heart failure, and in view of the fact that the patient continued to have frequent small emboli and petechiæ. On the 41st day of treatment, a hysterectomy was performed (Dr. W. Rubovitz), because of numerous moderately sized fibroids. The cord blood was sterile and penicillin was present in about one-half the concentration of the mother's blood, showing that the penicillin passes through the placenta, as has already been reported by Greene and Hobby.⁹ During the postoperative course, the patient continued to show several small petechiæ

but otherwise she was well. Therapy was stopped 15 days postoperatively. Blood cultures remained sterile and except for small petechiæ which have continued to appear since the completion of therapy, the patient has been well. She was discharged on the 75th hospital day and since has been doing light housework. There has been no recurrence for 12 months.

CASE 17. M. B., a 15 year old female with a history of chorea in 1938, was admitted on Feb. 20, 1945, with the complaints of fever and weakness of 8 weeks duration and pain in the plantar surface of the left foot of 3 days duration. On examination, there were several conjunctival petechiæ, a fading Osler node on the plantar surface of the first toe of the left foot, a markedly enlarged heart with an early high pitched diastolic murmur at the base and a presystolic crescendo murmur at the apex, and an enlarged spleen. The temperature was 102° F. Several blood cultures were positive for *Strep. viridans*, sensitivity to penicillin was 0.06 Oxford units. This was kindly determined by Dr. L. Loewe of Brooklyn Jewish Hospital, New York. The patient was given 8300 to 10,000 units of penicillin intramuscularly every hour day and night for 8 days with little clinical improvement. The dosage was then increased to 16,666 units intramuscularly every hour for another 6 days. Because of the relative resistance of the organism, 500,000 units per day were administered daily by the hourly intramuscular route for the next 41 days and 1 to 2 million units of penicillin daily by continuous intramuscular drip for 3 weeks. She was discharged on the 135th hospital day. There has been no recurrence for 8 months. However, the patient has had evidence of congestive heart failure and several pulmonary emboli. She has been bedridden for the last 3 months and auricular fibrillation has appeared.

Discussion. 1. *Efficacy of Penicillin Therapy.* Our series to date consists of 17 patients of whom 14 have fully recovered from their infection. All of them have been free from recurrences as of March 1, 1946 (Table 1), the longest follow-up being 20 months, the shortest 8 months. The patients have been closely followed after release from the hospital and all are afebrile, and their blood cultures remain negative. Their red blood count has returned to normal, the leuko-

cytosis has disappeared, and the sedimentation rate has fallen. Some have returned to their former occupation or to school. Of the remaining 3, 2 died during treatment, 1 discharged as a treatment failure died at home. One of the recovered patients died of congestive heart failure 8 months later and several others are suffering from this complication. It has been our experience as well as that of others^{4,16} that when the case has been adequately treated and has been "arrested" for a months, relapses have not as yet been observed.

The series is too small to be handled statistically but the results are in accord with those reported by others.^{1,3,4,16,18} This is particularly significant since the cases in this study were successive and unselected. There can thus be no doubt that penicillin offers a definite therapeutic approach to what has hitherto been almost invariably a fatal disease.

To obtain the best results, a proper method of penicillin therapy must be established and the factors which may reasonably be expected to influence the outcome should be defined. Some clues in regard to this have been obtained from our study and they will be briefly discussed. As experience grows, these factors undoubtedly will be subject to re-evaluation.

2. *General Condition of Patient.* This does not appear to play any definite part in his recovery. Thus 1 case (Case 14) with wasted atrophic muscles, abnormally low plasma proteins and anasarca—part of which was due to the low osmotic pressure of the plasma proteins—died on the thirteenth day of treatment. Another (Case 13) who was in excellent general condition required 112 million units of penicillin and several months of hospitalization before he responded to therapy. On the other hand Case 10, who was in poor general condition, made a speedy and uneventful recovery.

3. *Probable Duration of Infection.* In a disease like subacute bacterial endocarditis it is often difficult to state with exactness the day of onset. In 3 patients however,

the beginning of the disease followed immediately after teeth extraction. Prophylactic chemotherapy had not been given in these cases. The majority of our patients were ill from 4 to 16 weeks. The 2 who died during penicillin therapy (Cases 14 and 15) were ill for 44 and 40 weeks respectively before treatment was begun by us. Both had entered the ulcerative phase of the disease. It is our impression that the duration of the infection will not of itself alter the outcome of therapy providing complications such as ulcerations, perforations, mycotic aneurysm formation and congestive heart failure have not occurred. The chance of such complications occurring is greater of course the longer the disease continues.

4. *Nature of the Primary Disease.* Ten patients had rheumatic valvular disease, 4 had congenital heart disease (clinically diagnosed as a patent interventricular septal defect), 1 had combined congenital (a patent ductus arteriosus) and rheumatic heart disease, 1 had syphilis, and 1 had no apparent heart disease but a loud systolic murmur was present at the apex on admission. One of the cases with congenital heart disease and a complete heart block showed a prompt response after only 18 days of penicillin treatment. On the other hand, another case (Case 13) with the same congenital defect completed 145 days of treatment before it was successful. In the rheumatic valvular group, there was no correlation between valvular distribution and the effectiveness of therapy. Both fatal cases had combined mitral and aortic disease. The cases with aortic regurgitation however, which recovered from the infection were the ones which developed congestive failure readily.

5. *Resistance of Organism to Penicillin in vitro.* The susceptibility of the organism to penicillin is one of the most important factors in determining the outcome of therapy. In determining the sensitivities of the isolated strains of streptococci from blood cultures, various adaptations of the Oxford cup test⁷ and serial dilution

method⁵ were tried to determine the quickest way of obtaining clinically significant results with a minimum of the common sources of error. The one finally adopted was the serial dilution method. A control was made in each case with a standard strain of *Staphylococcus aureus* of a known sensitivity (Merck, *Staph. aureus* H MB109).

A concurrently run Oxford cup test sensitivity on several isolated strains correlated closely with the serial dilution method finding. The former method was found more practical in several cases where the strain was slow growing (48 to 72 hours). Sensitivities ranged from 0.015 to 0.08 Oxford units for bacteriostasis.

All the cases with strains of streptococci sensitive to less than 0.06 Oxford units responded to penicillin except 1. Case 15, with a sensitivity of 0.02 Oxford units died of a cerebral embolus during treatment. The therapy failures included Case 6 with a sensitivity of 0.06 Oxford units and Case 14 with a sensitivity of 0.08 Oxford units (died during therapy). It is safe to state that as a rule the more susceptible the organism is to *in vitro* penicillin action, the more prompt will be the response to therapy, barring complications. Exceptions, however, do occur. Above a certain *in vitro* penicillin sensitivity (over 0.06 Oxford units in our laboratory*) the cases respond with difficulty.

6. *Method of Administering Penicillin; Route, Dosage, and Duration of Therapy.* We have employed the following methods of administration of penicillin, viz.: (1) continuous intravenous or intramuscular drip, and (2) intermittent intramuscular injections.[†]

It was soon apparent that the use of a continuous drip method required constant attention day and night if the penicillin blood level was to be maintained uniformly high throughout the course of therapy. It has been shown²¹ that penicillin is quickly excreted. Like others therefore we have found[‡] that the blood level will quickly fall when the injection is stopped

* Our values run lower than determinations by Dr. Loewe's laboratory.

† In 2 patients intermittent "booster doses" as recommended by Baehr¹ were used.

‡ We employed a slight modification of the serial dilution method.

or the rate of administration decreased. Some patients cannot tolerate the continuous presence of a needle for days on end. In the case of the intravenous route a further disadvantage is that thrombophlebitis occurs and consequently all accessible veins may be eliminated. For this reason, and because less attention is required, we prefer the intramuscular to the intravenous route when a continuous drip is decided upon. Moreover, the blood levels maintained with the former are as high or even higher than with the latter.

In the case of intermittent intramuscular injections, the frequency of the injections should be such that the fluctuations of the blood level are slight. We have found, in confirmation of others,^{6,21} that there is little penicillin remaining in the blood serum 60 to 75 minutes after a single intramuscular injection and practically none at the end of 2 hours. The exact concentration varies, of course, with the amount injected and the rate of renal excretion. Fleming⁶ has shown that smaller doses given at more frequent intervals will maintain bacteriostasis in the blood for a longer period with the same total dosage than larger doses administered less frequently. Thus, intermittent injections at intervals of 3 or 4 hours are considered unsatisfactory when treating subacute bacterial endocarditis. Therefore, we have employed intermittent intramuscular injections *every hour on the hour day and night for the entire period of treatment*. This will maintain a high effective concentration at all times as we have verified by blood level determinations. We believe this is a satisfactory method and recommend it for future use. The total 24 hour dose is divided into 24 equal parts, each dissolved in 1 cc. of sterile physiologic saline and injected into the gluteal region. At first this may appear to be trying for the patient but within 1 or 2 days they become accustomed to the regimen and are no longer "needle conscious." While the fluctuations in penicillin concentration with this hourly method are greater than with the continuous drip method, the differences are not excessive. With the

higher daily dosages of penicillin (one million units or more) the continuous drip method is less wasteful of penicillin.

In 11 cases the hourly intramuscular injection schedule was employed. In the remaining cases interrupted intramuscular injection was combined alternately with continuous intravenous or intramuscular drip.

We agree with Loewe,¹⁶ that the best results are obtained when penicillin blood serum levels are maintained between 5 and 10 times the *in vitro* sensitivity figure. Such high levels are also desirable since there must be penetration of the vegetations and destruction of the organisms there located. The figures in our cases, given in Table 1, represent the lowest level of penicillin concentration in the serum during the 24 hour period when the hourly intramuscular injections were employed. These were obtained in all instances 55 minutes after the last hourly injection. During the first half hour after the injection the serum contained 4 to 10 times this minimal level. Even these levels are not always bactericidal for some strains of *Strep. viridans* but they are bacteriostatic. Thus, early during treatment we were able to obtain positive blood cultures in several cases when the anti-penicillin agent Clarase was added to the culture media.

The usual daily dosage was 200,000 to 300,000 units. At present we are giving larger daily doses to the more resistant cases (1 to 3 million units). The total amount of penicillin given ranged from 3.6 million units for the shortest treated case and 112 million units for the case requiring 145 days of treatment.

The usual course was planned for 21 days. The shortest successful treatment period was 18 days, the longest 145 days. Cases 3, 8, 10, 11 and 12 only required from 18 to 25 days of treatment with uniform success. On the other hand Case 6 was a treatment failure after 158 days of therapy.

The usual planned 3 week course of therapy was continued and the daily dosage increased when the clinical or bac-

terilogic response was unsatisfactory or when embolization, even though sterile, continued. The penicillin was stopped when blood cultures were consistently negative, when the general condition was greatly improved and when signs of active infection were no longer present as indicated by the white blood count, the sedimentation rate and the temperature curve. In 5 cases a slightly accelerated sedimentation rate (Wintrobe and micro-methods) persisted as the only abnormality for several weeks after therapy was completed, but in each instance it eventually returned to normal. If the organism is susceptible to the action of penicillin although more resistant than usual, viz., 0.06 Oxford units or more, we believe that treatment should be made continuous without interruption for longer than 3 weeks and larger daily dosages of penicillin should be used.

After therapy was stopped the patients were observed in the hospital, usually for about a fortnight with frequent blood cultures and other pertinent laboratory procedures before being discharged.

7. *General Measures Used to Supplement Penicillin Therapy.* All patients were placed on a palatable, high caloric, high vitamin diet (but no vitamins were added). The teeth were examined and cared for, and when indicated extractions were done, employing penicillin (5000 units per cc.) soaked sponges to pack the sockets. No untoward results followed the dental care. All cases received two or more transfusions of packed red cells at the beginning of treatment and iron therapy was used continuously in all cases. Bed rest was maintained at first, but as soon as feasible the patients were permitted increasing ambulatory privileges in the hospital.

8. *Response to Treatment and Complications During Treatment.* The rectal temperature curves of most of the cases fell precipitously to normal limits within 24 to 48 hours after penicillin was started with only an occasional slight evening rise to 100.4° F. during treatment, except when complications were present. The fall in temperature was associated with a

feeling of "well being" and an increased appetite, and a gradual disappearance of the café-au-lait color. The changes in the patients' personalities were striking; usually after 1 week a negativistic personality was replaced by a normal social temperament. The temperature curves of the fatal cases never reached normal during the treatment period. Some cases (Cases 1, 7 and 9) had a return to normal temperature by lysis. The temperature curve of Case 13 fell to normal during treatment, but immediately rose when the first and second courses were completed. The temperature curve of Case 6 fell to normal by crisis during some courses of therapy, but in others it remained elevated.

Anemia of varying degrees was present in practically all of the cases on admission to the hospital. As the infection was brought under control the red cell count and hemoglobin rose to normal levels.

Some of the complications encountered were incidental or coincidental to the endocarditis. Only one was directly attributable to the penicillin. This reaction consisted of a mild generalized urticaria responding to symptomatic treatment and did not interfere with the penicillin treatment. It occurred in Case 3, a child with hay fever and other allergic idiosyncrasies. It was the only untoward penicillin reaction found in our 17 cases, although we have given as much as 3 million units per day—this is certainly a tribute to the skill in preparing a highly purified penicillin.

One patient (Case 5) developed infectious mononucleosis on the 17th day of treatment. Still another (Case 8) was found to be a carrier of *E. histolytica*. Another (Case 13) was a carrier of *A. lumbricoides* and also had flagellates in his urine. Another patient (Case 9) had a positive Wassermann, Kahn and Eagle serologic tests before and after treatment which was shown at necropsy to be associated with syphilitic aortitis.

One patient (Case 16) was in the fourth month of pregnancy when admitted for treatment. After 6 weeks of penicillin therapy an abdominal hysterectomy was

advised because of a past history of several attacks of congestive heart failure. Her course following operation was uneventful except that after penicillin therapy was stopped she developed two petechiæ. She was afebrile, bacteria-free and asymptomatic, however, and has since remained well.

One other patient had an embolus to the posterior tibial artery after treatment was stopped, from which he quickly recovered. This was non-infected because repeated blood cultures at the time were negative and no signs of infection were present. It appears that during healing of the vegetations and after the vegetations are bacteria free, petechiæ and other embolic manifestations may occur. Petechiæ may reappear in some cases for months.

In 1 case (Case 15), an embolus to the left middle cerebral artery led to a massive cerebral hemorrhage on the 34th day of treatment after 11.4 million units of penicillin had been given. At necropsy friable vegetations (Fig. 4) were present on the right and non-coronary cusps of the aortic valve, from which *Strep. viridans* was obtained on culture; those present on the left cusp and chordæ tendinæ of the aortic leaflet of the mitral valve were fibrotic and calcified; perforation of this leaflet was also present. A mycotic aneurysm of the splenic artery and a large splenic "abscess" due to autolysis of septic infarcts were unexpected findings. *Strep. viridans* was cultured from the septic infarct.

The other fatal case (Case 14) died of congestive heart failure on the 13th day of treatment. His illness was of about 44 weeks duration and he had had congestive heart failure for some time as well as a long standing hypoproteinemia. Examination postmortem revealed ulceration and perforation of a bicuspid aortic valve (Fig. 5), and a mycotic erosive aneurysm of the anterior mitral leaflet (Fig. 6). Culture of the aortic valve revealed *Strep. viridans*. The vegetations on the aortic cusps were large and friable and showed little or no organization on histologic

study, whereas those on the mitral valve were small and firm and revealed moderate fibrosis. A right hydrothorax, ascites, chronic passive congestion of the viscera and septic myocardial infarcts were also present.

Case 6 had septic lung infarcts with empyema, *Bact. funduliformis* septicemia and also a relative renal insufficiency, all of which developed under treatment.

In several cases, especially these with aortic regurgitation, congestive heart failure developed when the patients became ambulatory. Three factors are probably involved: (1) the augmentation of the amount of regurgitation as the vegetations were healed, (2) the encroachment on the cardiac reserve as the patients became ambulatory, and (3) the myocarditis and myocardial fibrosis consequent to the infection. The failure has been progressive in some cases; it has required digitalis and mercurial diuretics. One patient (Case 17) has become bedridden on this account, and another (Case 9) died with it.

9. *The Rôle of Heparin.* Although our series is small, the results are as favorable as those reported on the combined use of heparin and penicillin.^{4,16} No one has actually proved the need of combining heparin with penicillin, nor have the theoretical considerations for its use been experimentally or clinically demonstrated. The view that it prevents further deposits of thrombotic material on the vegetations, or eliminates vegetations and thus facilitates healing directly, or that it facilitates penetration of penicillin or other chemotherapeutic agents into the vegetations is questioned (cf. 11). Embolization is not lessened by its use. In fact experience points to the contrary. More embolic deaths appear to have occurred in the presence of heparin when given intravenously than in its absence (cf. 11). It has not been demonstrated clinically that heparin acts in a synergistic manner with penicillin.

While final judgment must still be deferred, we do not at present recommend the use of an anti-coagulant because:

(a) The results with penicillin alone appear to be as favorable as those with penicillin plus heparin.

(b) The cost of therapy is increased by the use of heparin and its proper administration requires a more elaborate organization.

(c) Heparin often causes febrile reactions which obscure and confuse the clinical picture.

(d) Local pain is common following the subcutaneous administration of heparin.

(e) The intravenous use of heparin is hazardous (cf. 11).

Future efforts should be diverted in other directions, specifically in solving the problem of the cure of cases with strains of *Strep. viridans* which are more resistant than those usually encountered.

10. *Necropsy Evidence of Healing.* The findings in Case 9 are significant in proving by necropsy check that healing of subacute bacterial endocarditis is produced by effective penicillin therapy.

Summary and Conclusions. 1. Seventeen successive, unselected cases of bacterial endocarditis have been treated with penicillin alone. Fourteen cases have "recovered," the longest follow-up being 20 months, the shortest 8 months as of

March 1, 1946. Two cases have died during treatment and 1 case sent home as a treatment failure died at home. The autopsied cases showed infected vegetations at necropsy. One of the "recovered" cases developed progressive congestive heart failure, and died 8 months after "recovery." At necropsy a healing and healed endocarditis was found.

2. Eleven cases were treated exclusively by intramuscular injections of penicillin every hour day and night for 3 to 4 weeks using 200,000 to 300,000 units daily. We recommend this method for the average case since it maintains an adequate bacteriostatic penicillin level and it is effective. In the remaining cases, interrupted intramuscular injection was combined alternatively with continuous intravenous or intramuscular drip.

3. Cases with more resistant organisms (sensitivity 0.06 Oxford units or greater as determined in our laboratory) should receive larger daily dosages over longer periods of time.

4. Heparin was not employed in any case; we do not at present recommend its use.

5. Penicillin alone is an effective agent in the treatment of subacute bacterial endocarditis.

We wish to thank Drs. E. Davis, R. Herzog, M. Lev, J. Meyer, P. Rosenblum and S. O. Schwartz for referring private patients to us. The bacteriologic and hematologic studies were carried out with the technical help of Miss H. MacLean, A.B., and Mrs. R. Herzog, respectively.

REFERENCES

1. BAEHR, G.: Unpublished observations.
2. BEYER, K. H., FLIPPIN, H., VERWEY, W. F., and WOODWARD, R.: J. Am. Med. Assn., 126, 1007, 1944.
3. BLOOMFIELD, A. L., ARMSTRONG, C. D., and KIRBY, W. M. M.: J. Clin. Invest., 24, 251, 1945.
4. DAWSON, M. H., and HUNTER, T. H.: J. Am. Med. Assn., 127, 129, 1945.
5. FLEMING, A.: Lancet, 242, 732, 1942.
6. FLEMING, A., YOUNG, M. Y., SUCHET, J., and ROWE, A. J. E.: Lancet, 2, 621, 1941.
7. FOSTER, J. W., and WOODRUFF, H. B.: J. Bact., 46, 187, 1943.
8. FRIEDMAN, M., KATZ, L. N., and HOWELL, K.: Arch. Int. Med., 61, 95, 1938.
9. GREENE, H. J., and HOBBY, G. L.: Proc. Soc. Exp. Biol. and Med., 57, 282, 1944.
10. JORDON, E. O., and BURROWS, W.: Textbook of Bacteriology, Philadelphia: Saunders, 1943.
11. KATZ, L. N., and ELEK, S. R.: J. Am. Med. Assn., 124, 149, 1944.
12. KEEFER, C. S.: Am. Heart J., 17, 352, 1940.
13. KELSON, S. R.: Ann. Int. Med., 22, 75, 1945.
14. LIBMAN, E., and FRIEDBERG, C. K.: New York: Oxford University Press, 1941.
15. LICHTMAN, S. S.: Ann. Int. Med., 19, 781, 1943.
16. LOEWE, L.: Canad. Med. Assn. J., 52, 1, 1945.
17. LOEWE, L., ROSENBLATT, P., GREENE, H. J., and RUSSELL, M.: J. Am. Med. Assn., 124, 144, 1944.
18. MEADS, M., HARRIS, H. W., and FINLAND, M.: New England J. Med., 232, 463, 1945.
19. MOKOTOFF, R., KATZ, L. N., BRAMS, W., and HOWELL, K.: J. Am. Med. Assn., 126, 1167, 1944.
20. MOKOTOFF, R., KATZ, L. N., BRAMS, W., and HOWELL, K.: Proc. Cent. Soc. Clin. Res., 17, 49, 1944.
21. RAMMELKAMP, C. H., and KEEFER, C. S.: J. Clin. Invest., 22, 425, 1943.

OBSERVATIONS ON THE TREATMENT OF SCARLET FEVER WITH PENICILLIN

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In the treatment of hemolytic streptococcal infections of the throat, it is desirable to obtain not only a clinical cure, but also to eliminate the organisms from the patient's nose and throat to prevent the establishment of a convalescent carrier state. This is especially true in military populations and wherever there is a rapid turnover of personnel. Many workers have demonstrated the failure of sulfonamides, either in therapeutic or prophylactic doses to prevent or cure the "Strep. carrier."^{1,3,5,7} Recently, however, reports^{2,4} have commented on the efficacy of penicillin therapy in the treatment of streptococcal pharyngitis and scarlet fever, and Plummer⁶ has reported a small series of patients with streptococcal pharyngitis and tonsillitis treated with varying doses of penicillin. He was able to demonstrate that recurrent positive throat cultures developed in 8 of 9 patients treated with 100,000 to 150,000 units over a 1-day period; in 4 of 9 patients treated with 240,000 units over 3 days; and in but 1 of 10 patients treated with 540,000 units over a 6-day period.

It was believed to be of value to determine not only the minimal effective dosage of penicillin in the treatment of scarlet fever, but also that necessary for the elimination of the convalescent carrier phase. A total of 118 patients were available for this study over the period of February to June 1945.

All patients in the series were enlisted Naval personnel, young and in good health. A diagnosis of scarlet fever was based on the clinical picture of pharyngitis, fever

and a typical rash; and in 76% of the cases, the initial throat culture was positive for beta hemolytic streptococci. The plan of therapy utilized 3 dosage schedules of penicillin as follows:

1. Total dosage 240,000 units: 10,000 units every 3 hours, or 80,000 units per day for 3 days.

2. Total dosage 360,000 units: 10,000 units every 3 hours or 80,000 units per day for 3 days; then 10,000 units every 6 hours or 40,000 units per day for 3 days.

3. Total dosage 480,000 units: 10,000 units every 3 hours or 80,000 units per day for 4 days; then 10,000 units every 6 hours or 40,000 units per day for 4 days.

Patients were housed in covered cubicles containing 5 patients each, under isolation and with minimal outside contacts. Throat cultures were taken on the day of admission and every 2 to 3 days for the duration of their stay in the hospital, which was 14 to 21 days. The post therapy follow up varied from 2 days to 2 weeks, and all patients were kept on isolation during the period. Penicillin (Eli Lilly) was the preparation used.

Results. The results were judged by: (a) the clinical response to therapy; (b) the percentage of complications after therapy; (c) the development of positive throat cultures following each of the 3 dosage schedules.

Clinical Response to Therapy. All cases treated with penicillin showed a good clinical response, in that the temperature dropped to normal and there was marked symptomatic improvement in 24 to 48 hours. Although several cases showed a

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† This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the U. S. Navy. The opinions and views set forth in this article are those of the writer and are not to be considered as reflecting the policies of the Navy Department.

few residual organisms on the second day of therapy, all but 1 of the 118 cases had a negative throat culture during the course of penicillin therapy, regardless of the total dosage. Complications did not develop in any case during the therapy.

Incidence of Complications. Any rise in temperature (after completion of therapy) accompanied by recurrence of rhinitis, otitis media, sinusitis, or adenitis was considered to be a complication. The incidence of complications was highest (31%) in the 240,000 unit series and lowest (6%) in the 480,000 unit series (Table 1). Each

period than those with negative cultures. The follow-up period was divided into 4 day intervals, and among the patients observed through each of these periods, the number of those developing positive throat cultures was determined. It is clear that, in the 480,000 unit series, despite a higher percentage of initial positive cultures, there was a marked reduction in the incidence of recurrent positives after completion of therapy. A group of 12 of these patients was followed for a 2 week convalescent period of hospitalization, and cultures taken over this period

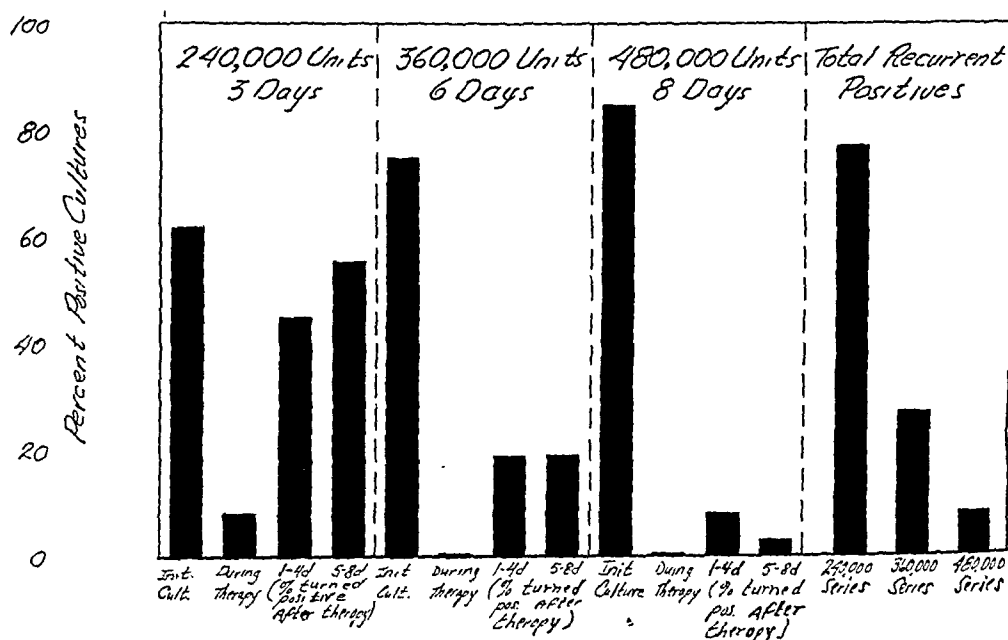


CHART 1.—Recurrence of positive throat cultures after penicillin therapy in scarlet fever.

one of these complications in a patient was found to be accompanied by a recurrence of a positive throat culture.

Effect on Throat Cultures. The effect of varying dosages of penicillin on throat cultures taken after cessation of therapy is shown on Table 2 and Chart 1. The method of analysis described was necessary since the follow-up period on each patient varied and patients with positive cultures and recurrent symptoms were hospitalized and followed for a longer

period than those with negative cultures. The overall incidence of recurrent positive throat cultures (Tables 2 and 3) demonstrates clearly the effectiveness of the 480,000 unit dosage scheduled in the maintenance of negative throat cultures in convalescent patients. Those turning positive were but mildly ill, i. e., carriers only.

*Typing and Sulfonamide Resistance Studies.** Typings were obtained on 57 of

* Streptococcal typings and resistance studies were kindly done by Lt. Comdr. Armine Wilson, (MC) USNR, Streptococcal Typing Laboratory, National Naval Medical Center, Bethesda, Md.

the 90 initial positive throat cultures and of this group, 25 were tested for sulfonamide resistance. The results of these studies are shown in Table 4. If these typings can be considered representative of the entire series, about 60% of the infections in this series were due to Type "A" Group 17, and 28% were due to Type "A" Group 19. Together, these two types were isolated from 89% of the cases.

Sulfonamide resistance studies on these strains revealed that 17 out of the 18, or

95% of the Type 17 organisms were resistant to 'sulfonamides in a concentration of 25 mg. per 100 cc.. Of all the organisms tested, 72% showed sulfonamide resistance. This high incidence of sulfa-resistant strains of organisms well emphasizes the need of penicillin therapy in treatment of patients with streptococcal disease.

In 9 instances it was possible to obtain typings of the initial positive culture and of recurrent positive cultures. These results are shown in Table 5. In 8 out of

TABLE 1.—INCIDENCE OF COMPLICATIONS

Dosage series	No. cases	Recurrent symptoms	% complication
240,000 un., 3 days . . .	26	8	31
360,000 un., 6 days . . .	44	6	14
480,000 un., 8 days . . .	48	3	6

TABLE 2.—RECURRENCE OF POSITIVE THROAT CULTURES AFTER PENICILLIN THERAPY (OVER 4 DAY FOLLOW-UP PERIODS)

Dosage series	% pos. at onset	1-4 days		5-8 days		9-12 days		12 days +	
		Cases observed	% pos.*	Cases observed	% pos.*	Cases observed	% pos.*	Cases observed	% pos.*
240,000 un., 3 days . . .	62	21	45	15	53	2	100	—	—
360,000 un., 6 days . . .	75	43	19	21	19	2	0	1	0
480,000 un., 8 days . . .	85	39	8	28	4	10	0	12	0

* % turned positive during each 4 day follow up period.

TABLE 3.—OVERALL RECURRENCE OF POSITIVE THROAT CULTURES AFTER PENICILLIN THERAPY

Dosage series	Cases	% positive at onset	% positive after therapy
240,000 un., 3 days . . .	26	62	77
360,000 un., 6 days . . .	44	75	27
480,000 un., 8 days . . .	48	85	8

TABLE 4.—TYPING AND SULFONAMIDE RESISTANCE STUDIES

Type	Not sulfa-resistant	Resistant (to 25 mg. Per 100 cc.)	% sulfa-resistant	Resistance not determined	Total typed	% of total cases
A-17	1	17	95	17	35	61
A-19	2	1	33	13	16	28
A-30	3	0	0	1	4	7
Others	1	0	0	1	2	4
Total	7	18	72	42	57	100

TABLE 5.—COMPARISON OF STREPTOCOCCAL TYPES ISOLATED FROM INITIAL THROAT CULTURES WITH THOSE ISOLATED FROM RECURRENT POSITIVE THROAT CULTURES

Series	Case No.	Initial type	Recurrent type
240,000 un., 3 days	I-3	A-17	A-17
	I-8	A-17	A-17
	I-9	A-17	A-17
360,000 un., 6 days	II-2	A-17	A-17
	II-3	A-17	A-17
	II-31	A-17	A-17
	II-12	A-30	A-30
480,000 un., 8 days	III-1	A-17	A-17
	III-2	A-17	A- 6

9 instances, the recurrent type was the same as the initial type. In 1 instance, Case No. 2 in the 480,000 unit series, the recurrent type was different from the initial type, indicating a new infection. In the other instances, because of high incidence of Type 17 in this series, it could not be determined whether results represented a new infection or a recurrence.

An attempt was made by *in vitro* studies to determine the possibility of penicillin resistant strains of streptococci in some of the patients in the series, but no evidence for such could be found.

Discussion. With the development of strains of streptococci resistant to the action of sulfonamides, 2 problems arose in the treatment of scarlet fever: (1) the clinical response to sulfonamides was delayed or absent, and (2) throat cultures remained positive for beta hemolytic streptococci, despite sulfa therapy. These convalescent carriers were disseminating virulent organisms back into their environment, thus acting as foci for the spread of further streptococcal disease. The sensitivity of the streptococcus to penicillin made the drug an ideal agent for the treatment of streptococcal disease and for the elimination of the organisms from the throats of convalescent patients. In the control of respiratory disease in groups of men, it is this latter problem, the elimina-

tion of the convalescent carrier phase, that becomes especially important. There are perhaps other and possibly more effective ways of using penicillin for this purpose. This study, however, represents our past experience in the search for an optimal dosage schedule.

Summary and Conclusions. 1. Three series of scarlet fever patients were treated with increasing dosages of penicillin: 240,000 units over a 3 day period; 360,000 units over a 6 day period; and 480,000 units over an 8 day period.

2. The clinical response to penicillin was good in all cases.

3. The incidence of complications was highest (31 %) in the 240,000 unit series, and lowest (6 %) in the 480,000 unit series.

4. The rate of recurrence of positive throat cultures was highest (77 %) in the 240,000 unit series, and lowest (8 %) in the 480,000 unit series.

5. Of the organisms found, 89 % were Types A-17 and A-19. Of the organisms typed, 72 % were resistant to sulfonamides in concentration of 25 mg. per 100 cc. or more.

6. The use of 480,000 units of penicillin over an 8 day period is a satisfactory method for the treatment of scarlet fever, and for preventing the establishment of a beta hemolytic streptococcus carrier state in the convalescent patients.

NOTE: During the month of September, 1945, 12 patients with scarlet fever were treated with 480,000 units of penicillin over a 3 day period (20,000 units every 3 hours for 3 days). In this group, throat cultures on all patients were positive for beta hemolytic streptococci at the onset and became negative during therapy. Recurrent positive throat cultures were obtained on 11 patients within 8 days following the cessation of therapy. Of these patients, 6 required a second course of penicillin therapy because of recurrence of clinical symptoms. These data suggest that in the treatment of streptococcal infection with penicillin, the duration of therapy is as important as the total dosage of penicillin used.

REFERENCES

1. CARTER, T. J., COBURN, A. F., *et al.*: The Prevention of Respiratory Tract Bacterial Infections by Sulfadiazine Prophylaxis in the United States Navy, *Nav. Med.*, 284, p. 157.
2. CRAIG, W. M., *et al.*: Penicillin: A Progress Report Based on 1455 Cases Treated at the National Naval Medical Center, Bethesda, Md., *U. S. Nav. Med. Bull.*, 44, 453, 1945.
3. JULIANELLE, L. A., and SIEGEL, M.: The Epidemiology of Acute Respiratory Infections Conditioned by Sulfonamides. II. Gross Alterations in the Nasopharyngeal Flora Associated With Treatment, *Ann. Int. Med.*, 22, 10, 1945.
4. KEEFER, C. S., HERWICK, R. P., VAN WINKLE, W., and PUTNAM, L. E.: The Dosage of Penicillin, *J. Am. Med. Assn.*, 128, 1161, 1945.
5. PLUMMER, N., and SMILLIE, W. E.: Sulfadiazine in the Treatment of the Common Cold, *J. Am. Med. Assn.*, 124, 8, 1944.
6. PLUMMER, N., DUERSCHNER, D. R., WARREN, H. D., ROGLIANO, F. T., and SLOAN, R. A.: *J. Am. Med. Assn.*, 127, 369, 1945.
7. RHODES, P. S., and AFREMOW, M. L.: Sulfanilamide in the Treatment of Sore Throat Due to Hemolytic Streptococci, *J. Am. Med. Assn.*, 114, 942, 1940.

SLOWLY PROGRESSIVE OCCLUSIVE THROMBOSIS OF THE ABDOMINAL PORTION OF THE AORTA

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OCCLUSION of the abdominal portion of the aorta may occur by emboli lodging at the bifurcation of the aorta, by acute or rapidly progressive thrombosis, by thrombi developing on emboli and by chronic or slowly progressive thrombosis. The symptomatology presented by these entities varies according to the rate of development and extent of the lesion: those associated with rapidly progressive occlusion present a relatively clear cut diagnostic clinical picture; but the clinical findings of the slowly progressive occlusion are insidious and easily overlooked. Three cases in the latter group are presented with emphasis on the clinical recognition of the condition.

Clinical Abstracts. CASE 1. S. S., a 52 year old white woman, had multiple hospital admissions and visits to the Out-Patient Department of the St. Luke's Hospital for unrelated conditions. Fortunately, through contacts by multiple hospital admissions and visits to the Out-Patient Department, a fairly detailed record of the patient had been maintained. On Jan. 13, 1938, fixed parametrial tissue, a mass in the cul-de-sac, and a bloody vaginal discharge were found and a clinical diagnosis of "carcinoma of the cervix, stage four" was made. No biopsy was taken. The patient was referred to the Roentgenologist for deep therapy. She received 2450 "R" units from Jan. 19 to March 1, 1938. No radium was inserted. The blood pressure, frequently recorded, was never higher than 130/90 mm. Hg. Eighteen days after the last Roentgen ray treatment there developed pain in the left leg and black discoloration of the third toe of the right foot.

It was then revealed, for the past several years she had suffered with varicose veins in both legs and had experienced severe pain on walking. Pressure over the tibias and calf muscles also elicited moderate pain. Her blood pressure was 135/88. With the diagnosis of peripheral arteriosclerotic disease she was given daily Pavex treatments to both feet without appreciable benefit.

In the following 2 months the gangrene extended slightly, both feet became slightly cyanotic and cold, the right somewhat worse than the left, and no pulse could be felt in either foot. Blood pressure on May 18, 1938 was recorded at 164/92. Because of severe pain as well as the gangrene the right lower extremity was amputated through the middle of the leg. Examination of this specimen showed no arteriosclerosis. The operative stump became gangrenous necessitating re-amputation through the middle of the thigh 1 month later. This specimen revealed old thrombosis of the femoral artery and recent thrombosis of other arteries and veins.

In August, 1939 she reappeared complaining of pain in the right parietal region of her head, dizziness and occasional vomiting for the past 3½ months. At this time her blood pressure was 195/120. The blood vessels in the fundi of her eyes were moderately sclerotic. There was moderate cyanosis. No arterial pulsations could be felt at the knee or ankle of the left lower extremity. Clinical diagnoses of generalized arteriosclerosis, hypertensive cardiovascular disease with possible prodromata of "stroke" and thrombosis of left femoral blood vessels were made. The patient was last admitted on Oct. 5, 1939 for treatment of a chronic cystitis. Following cystoscopy a retroperitoneal pelvic cellulitis developed. The patient died 3 days

later. The highest recorded blood pressure, 250/110, was found on Oct. 14, 1939, the day of her death.

Autopsy. The autopsy revealed an extensive retroperitoneal abscess in the pelvis extending along the left psoas muscle. The origin of the abscess could not be traced. There was a considerable degree of chronic hemorrhagic cystitis and purulent urethritis but no perforation of the wall. No evidence of carcinoma could be seen in the pelvis or genitalia.

The aorta, from the bifurcation to the level of the lower border of the ostium of the celiac artery, was completely occluded by an old thrombus. This portion of the aorta was moderately constricted, measuring only 1.4 cm. in diameter. The wall at this level revealed a moderate degree of arteriosclerosis. The patent portion of the aorta presented only slight atherosclerotic change. The thrombus extended into both common and internal iliac arteries, into the left external iliac artery and the proximal 0.5 cm. of the right external iliac artery. The orifice of the left renal artery was partially obstructed by the aortic thrombus, but the right renal artery was completely occluded in the proximal 1 cm. The inferior mesenteric artery was also completely occluded.

A moderate reduction in size of the right kidney (70 gm.) was attributed to extensive ischemic atrophy. The left kidney presented a severe acute passive congestion and a moderate compensatory hypertrophy (210 gm.). The arterioles of both kidneys were unaltered, but the small and moderate sized arteries revealed a moderate degree of sclerosis. No nephrosclerosis had developed. A few old infarcts were noted in the spleen. The heart weighed 350 gm., indicating only a slight amount of hypertrophy. No abnormality could be seen in the other abdominal viscera or in the lungs or brain.

Though the aortic thrombosis in this case was not the cause of death, the onset of the hypertension is believed to have occurred when the aortic thrombus involved the orifices of the renal arteries. The relation between the two will be discussed below. The death here was due to the extensive retroperitoneal suppurative cellulitis.

CASE 2. J. S., a 54 year old white man, was first seen in the diabetic out-patient clinic of the Cedars of Lebanon Hospital in June 1935, with intermittent claudication

and paresthesias of both feet and a feeling of great weakness of the legs after moderate exercise. He had been known to have diabetes mellitus for about 2 months. At that time, his blood pressure was 150/90 mm. Hg. Pulsations were noted to be distinctly diminished in the posterior tibial arteries at this time. Treatment was symptomatic.

About 1 year later, he was transferred to the peripheral vascular disease clinic with the same complaints. Thermocouple readings at that time showed a drop in temperature from the mid-portion of both legs to the feet. The large toe and plantar aspect of both feet registered a reading of -2 and -3.5° respectively. The legs were pale and blanched when elevated, becoming slightly cyanotic when dependent. A dorsalis pedis pulse was noted in the right foot but not in the left. No records were made of the other pulses at this time. The patient was treated with hypertonic sodium chloride solutions intravenously but without beneficial effect.

During the following year, it was noted that except for the femorals no pulsations were palpable in either lower extremity and areas of partial anesthesia developed on the lateral aspect of both ankles. No trophic disturbances were seen.

Shortly thereafter he was referred to the cardiac clinic because of angina pectoris and exertional dyspnoea. There he was followed rather closely for the next 2 years. A diagnosis of arteriosclerosis of the coronary arteries with myocardial fibrosis was made, supported by electrocardiographic changes. During this period the blood pressure rose from 140/90 to 190/100 mm. Hg.

In 1942 symptoms of cardiac failure developed and the patient was first admitted to the medical service of the Cedars of Lebanon Hospital in March of the same year. Physical examination revealed moderate peripheral edema and pulmonary edema. Again it was noted that the arterial pulses were absent in both lower extremities. Treatment was symptomatic and recovery excellent so the patient was discharged to a rest home in 1 week.

He was readmitted to the hospital 11 months later with recurrence of his cardiac failure. This time there was auricular fibrillation and response to therapy was slower.

His final admission to the hospital occurred in July of 1943. He had been awakened from a sound sleep by an overpowering

pain in the abdomen which made him feel faint. His wife, terrified by his ashen pallor and listlessness, secured immediate medical aid and he was admitted to the hospital 3 hours later. At that time he was in deep shock. The abdomen was distended with moderate generalized tenderness, but no rigidity could be found. He died 14 hours later, still in profound shock.

Autopsy. Autopsy revealed an extensive hemorrhagic infarction involving practically all of the small intestine and the cecum. The diameter of the lower half of the abdominal portion of the aorta was moderately smaller than that at any point proximal to it. There was a marked ulcerative arteriosclerosis of the aorta, most pronounced, as usual, in the abdominal portion. A large firm thrombus with moderately advanced peripheral organization completely filled the lower half of the abdominal portion of the aorta, obliterating the orifice of the inferior mesenteric artery, extending distally into both common, internal and external iliac arteries and into the proximal portion of the femoral arteries. Proximally, the thrombus completely filled the aorta to a point just below the orifices of the renal arteries. Above this level, the anterior portion of the thrombus extended along the aortic wall between the orifices of both renal arteries, partially occluding that of the left renal artery, to reach the orifice of the superior mesenteric artery which it completely occluded. The proximal 5 cm. of the superior mesenteric artery was filled with a fresh thrombus.

The heart weighed 590 gm. It was moderately hypertrophied and revealed severe coronary arteriosclerosis with atherosclerotic occlusion, an old healed myocardial infarct with aneurysmal dilatation of the ventricular wall, and organizing mural thrombi in both the left ventricle and left atrium.

The spleen and the left kidney presented a few old healed infarcts. Those in the kidney could have resulted from embolic pieces of thrombotic material from the aorta, while those in the spleen would have resulted more likely from the mural thrombus in the heart.

Only a minimal degree of sclerosis of the large intrinsic renal arteries was observed.

The death of this patient was undoubtedly due to a slowly progressive thrombosis of the abdominal portion of the aorta, developing on the severe aortic sclerosis, complicated

by a hemorrhagic infarction of the intestinal tract when the thrombus occluded the superior mesenteric artery. Postmortem blood culture revealed a *B. welchii* septicemia. The hypertension could have developed, as in the previous case, at the time of the partial occlusion of one renal artery by the aortic thrombus. The relation between the two will be discussed below.

CASE 3. J. H., a 53 year old white man, was admitted to the Cedars of Lebanon Hospital with dyspnea and orthopnea in October 1942. For a year before admission he had suffered from weakness and exertional dyspnea and occasional dizzy spells. He volunteered no complaints referable to his lower extremities.

His blood pressure was 240/110 mm. Hg on admission. The heart was large and the rhythm regular. The rate was 100 per minute. A systolic murmur could be heard. Fine râles were present throughout both lung fields. No pulses were noted in either lower extremity. The blood Wassermann and Kline tests were positive.

The patient was responding relatively well to therapy for hypertensive cardiac failure when suddenly he had a short generalized convulsion which passed off rapidly. Five minutes later, he had a few more clonic convulsions and died.

Autopsy. At autopsy, marked arteriosclerosis of both the thoracic and abdominal portions of the aorta was present. Many of the arteriosclerotic plaques were ulcerated. The lower two-thirds of the abdominal portion of the aorta and the common iliac arteries were completely occluded by a sandy brown thrombus with peripheral fibrosis. It extended up to the level of the renal arteries partially occluding the orifices of both. There was a small accessory renal artery on the left which was not occluded. The orifice of the superior mesenteric artery was not involved by the thrombus.

The heart weighed 660 gm. It was considerably hypertrophied and repeated section showed no evidence of fibrosis. The coronary arteries revealed only slight sclerosis with slight focal stenosis of their lumina.

The kidneys were of average size and presented moderate arteriolar and arterial nephrosclerosis.

The brain showed considerable sclerosis of the basilar and intrinsic arteries. Their lumina were considerably stenosed but not

thrombosed. Repeated coronal section of the brain revealed small areas of encephalomalacia involving chiefly the basal ganglia and pons.

Examination of the other organs of the body did not add to the evaluation of the case.

The death of this patient was apparently due to cerebral arteriosclerosis with multiple areas of encephalomalacia complicated by hypertensive cardiac failure. As in the first case the aortic thrombosis here did not contribute directly to the death of the patient. Though a moderate degree of arterial nephrosclerosis was present, the encroachment of the aortic thrombus on the orifices of the renal arteries may have a causal relationship to the hypertension as will be discussed below.

Discussion. Occlusion of the lower portion of the abdominal aorta may occur in a variety of ways, the symptomatology being determined essentially by the rate and extent of the process. Emboli, most commonly from endocardial thrombi, lodging at the bifurcation produce the most common type of occlusion with well recognized and dramatic clinical findings. Gangrene usually develops, is bilateral and usually located below the knees.¹⁵ Paresis and anesthesia, due to ischemia of the spinal cord are relatively constant.²⁰ There are numerous reports on the recognition and successful treatment of this type of aortic occlusion.^{1,2,15,20,24}

Acute or rapidly progressive thrombosis of the abdominal portion of the aorta produces essentially the same symptomatology. It may be superimposed on embolism which incompletely occludes the aorta at the bifurcation or the iliac arteries;²⁰ it may result from infection of the umbilicus in infants with subsequent septic thrombosis of the umbilical and hypogastric arteries;^{16,25} it has been reported in luetic aortitis,⁸ rheumatic fever and other acute infections.²⁰ In this type of thrombosis, in addition to the effect on the lower extremities, the rapid progression of the thrombus proximally leads early to infarction of the abdominal viscera and death.

On the other hand, slowly progressive occlusive thrombosis of the abdominal portion of the aorta is uncommon. It is of insidious onset and of long duration, usually a number of years. Due to inadequate differentiation in much of the literature between these types of aortic occlusion, it is difficult to attempt to determine the total number of recorded cases of the chronic form. Some idea of its frequency may be secured from several sources. Among 1500 consecutive autopsies at the Cedars of Lebanon Hospital, only 2 cases were seen. Siegel and Garvin²² found 9 cases in 6457 autopsies performed at the Cleveland City Hospital. Bull⁸ states that he has found 9 cases of complete thrombosis of the abdominal aorta in 6000 autopsies. Lueth reported 1 case in 1047 autopsies at the Research and Educational Hospital.¹⁴ From these figures the mean incidence is approximately 0.12%. Males are more frequently affected than females.

This type of aortic thrombosis is usually a complication or sequela of arteriosclerosis of the aorta as it was in the 2 cases seen at the Cedars of Lebanon Hospital. Its predilection for the abdominal portion of the aorta is probably best explained by the fact that atheromatosis is most advanced in this area and is facilitated to some extent by eddies set up by the division of the current of blood at the bifurcation. The thrombosis probably first occurs in an ulcerated atheromatous plaque, being, in its early stages, mural in nature, and with further superimposed thrombosis, the entire aortic lumen is occluded. A study of this process has been reported by Clark *et al.*⁴ Sauer²¹ believes that occasionally recovery may occur from the immediate effects of embolism of the aortic bifurcation and that the picture of chronic occlusive thrombosis then may be superimposed. He is supported in this contention by 2 other cases,^{6,20} but this mechanism is distinctly infrequent. In the first case described by us, though it cannot be proved, there is a strong possibility that the thrombosis was initiated

by the Roentgen radiation, probably assisted by the retroperitoneal inflammation since neither of these processes alone are known to thrombose large arteries. This mechanism for the production of aortic thrombosis is undoubtedly rare. In almost all reported cases, including ours, the thrombosis extended into both common iliac arteries, the internal and external iliac arteries and at times into the femoral arteries. Proximally the thrombus has been found as high as the level of the ostium of the superior mesenteric artery.

The early symptoms of this occlusion of the aorta result from the inadequate blood supply to the lower extremities, to the lumbar portion of the spinal cord and possibly to the pelvic organs. Many of these clinical findings are among those commonly complained of by elderly people and unless aortic thrombosis is suspected it is apt to pass unrecognized. Many of these patients, including those reported here, complained of disturbances in the lower extremities commonly associated with peripheral arterial disease, such as intermittent claudication, coldness of the feet, and cyanosis of the feet on exercise. An important clinical clue in favor of the thrombosis of the aorta, however, lay in the fact that the popliteal and posterior tibial arterial pulses were completely absent bilaterally. In peripheral vascular disease such equality may occur but is not ordinarily seen. In some of these cases, and in 1 of ours (J. S.), femoral arterial pulses were recorded, but which in retrospect probably were transmitted impulses from the aorta. Gangrene of the extremities may, but usually does not, result from slowly progressive thrombosis of the aorta because of the time factor which permits the development of collateral circulation. Case 1 of our group which did develop gangrene probably exemplifies the exception, and may have been due to a more rapid progression of the occlusive thrombosis in this case than in the other cases.

Déjérine's syndrome,²³ originally described in luetic arteritis affecting the lumbo-sacral arteries, consists essentially

of a paresis of the lower extremities, brought on by exercise and relieved by rest. This syndrome results from inadequate arterial supply to the lower segments of the spinal cord.

Reichert, Ryland, and Bruck¹⁷ have described a similar condition in arteriosclerosis of those blood vessels and have reproduced the syndrome by ligation of either the lumbo-sacral arteries or the abdominal portion of the aorta. It is of interest to note also that when the abdominal portion of the aorta is occluded in dogs, the most troublesome consequence is paresis of the lower extremities, particularly after exercise.⁹ Gangrene does not result.

One of the patients (J. S.) presented a story very suggestive of Déjérine's syndrome and it is quite possible that had it been sought in the other cases, a similar history might have been obtained.

LeRiche¹³ also described, among more than 20 cases of chronic occlusive thrombosis of the aorta, "extreme fatigability" of the lower extremities, which suggests Déjérine's syndrome. He also reported that he had seen no trophic disturbances. To the symptoms so far described, LeRiche adds impotence as another, which he ascribes to a deficient blood supply to the penis but which, in our opinion, could be due just as likely to the ischemia of the spinal cord or sympathetic nerves controlling erection of the penis.

As long as the aortic thrombus remains below the level of the renal arteries, the disease is only moderately incapacitating and in itself is not a threat to life. Apparently occlusion of the orifice of the inferior mesenteric artery as in our cases and in several of the reported cases^{5,14,19} produces no infarction of the intestine. However, as the thrombus extends proximally, it may produce a stenosis or occlusion of the orifices of the renal arteries or of the superior mesenteric artery.

As the thrombus occludes the renal arteries portions of the thrombus may break off and embolize to the kidney,

resulting in infarcts. The presenting symptom in such cases may be hematuria.

This is exemplified in 1 of our cases (No. 2) and in cases described by Siegel and Garvin,²² Doane and Blumberg⁵ and Hamilton.¹⁰ In our cases and in 2 other reports in which partial occlusion of the renal orifice was observed,^{12,18} a pronounced hypertension was also present. The cases reported by us presented variable degrees of occlusion of the renal arteries from partial to complete. Case 1 was closely followed and the onset of a progressive hypertension was observed about 1 year prior to death. In this case particularly it appears as though the onset of the hypertension is coincidental with the stenosis of the renal arteries by the thrombus. Case 2, which was uncomplicated by nephrosclerosis also strongly suggests a relationship between the stenosis of the renal artery orifice and the hypertension. In Case 3 the nephrosclerosis alone could have accounted for the hypertension but the rôle of the aortic thrombus occluding the renal artery orifice in causing or contributing to the hypertension cannot be entirely excluded. This partial occlusion of the renal arteries by thrombi, with resultant renal ischemia, are relatively close clinical analogies to the renal ischemia with resultant hypertension produced experimentally in dogs by means of a stenosing clamp on the renal arteries as described by Goldblatt.⁷

As in 1 of our cases (J. S.) and in others culled from the literature,^{1,12,24} the thrombus may extend along the aortic wall between the orifices of the renal arteries and may occlude the orifice of the superior mesenteric artery. In such cases, the terminal clinical picture is that of intestinal infarction produced by either throm-

bosis of the mesenteric artery or embolism by a piece of the aortic thrombus.

The time interval between the onset of the early signs and symptoms of chronic aortic thrombosis and the onset of visceral involvement is usually quite long. In 1 of our cases (J. S.) which is quite representative, this time interval was approximately 5 years.

The only attempt at therapy in chronic occlusive thrombosis of the aorta has been made by LeRiche.¹³ In the early stages, when the diagnosis is made, he recommends resection of the thrombosed portion of the aorta and iliac arteries, apparently to prevent proximal extension of the thrombus, and also resection of the first and second lumbar ganglia. He states he has performed either one or both of these procedures in 5 patients, but unfortunately his report is not sufficiently detailed to permit critical evaluation of his results.

Summary and Conclusions. Three cases of slowly progressive occlusive thrombosis of the abdominal portion of the aorta are presented. The disease is usually secondary to a severe ulcerative arteriosclerosis of the arterial wall, but may follow an embolism to the bifurcation of the aorta, or more rarely, thrombosis of the pelvic arteries after irradiation. Its mean autopsy incidence is 0.12%. The characteristics of this syndrome that permit differentiation from other forms of aortic occlusion are: insidious onset; protracted course; usually, but not always, absence of gangrene; absence of pulses in both lower extremities; weakness in legs after exercise with recovery on rest; and the appearance of arterial hypertension or of signs of visceral infarction years after the signs of muscular insufficiency in the lower extremities were first experienced.

REFERENCES

1. BANOWITCH, M. M., and IRA, G. H.: *Med. Clin. North America*, **11**, 973, 1928.
2. BREWSTER, E. S.: *J. Iowa Med. Soc.*, **31**, 12, 1941.
3. BULL, P.: Quoted by Doane and Blumberg.⁵
4. CLARK, E., GRAEF, I., and CHASSIS, H.: *Arch. Path.*, **22**, 183, 1936.
5. DOANE, J. C., and BLUMBERG, N.: *Med. Clin. North America*, **19**, 159, 1935.
6. FRY, F. W.: *Am. Heart J.*, **18**, 57, 1939.

7. GOLDBLATT, H.: Harvey Lectures, 1937, 1938; *Am. J. Clin. Path.*, **10**, 40, 1940.
8. GOUGH, J.: *Lancet*, **2**, 21, 1935.
9. HALSTEAD, W. S.: *J. Exp. Med.*, **11**, 373, 1909.
10. HAMILTON, J. F.: *South. Med. J.*, **23**, 532, 1930.
11. HESSE: Quoted by Ira and Banowitch.¹
12. KELTY, R. A.: *Med. Rec.*, **92**, 19, 1917.
13. LE RICHE, R.: *Presse méd.*, **48**, 601, 1940.
14. LUETH, H. C.: *Ann. Int. Med.*, **13**, 1167, 1940.
15. MASON, R. L., and WARREN, S.: *New England J. Med.*, **204**, 1129, 1931.
16. MOSCHOWITZ, E.: *Proc. New York Path. Soc.*, **14**, 21, 1914.
17. REICHERT, F. L., RYTAND, D. A., and BRUCK, E. L.: *AM. J. MED. SCI.*, **187**, 794, 1934.
18. RONALD, J., and LESLIE, M.: *Glasgow Med. J.*, **134**, 7, 1940.
19. ROSENBERG, E. F., KEITH, N. M., and WAGNER, H. P.: *Arch. Int. Med.*, **62**, 461, 1938.
20. ROTHSTEIN, J. L.: *Am. J. Dis. Child.*, **49**, 1578, 1935.
21. SAUER, D.: *Trans. West Surg. Assn.* (1941), **51**, 446, 1942.
22. SIEGEL, M. L., and GARVIN, G. F.: *Ohio State Med. J.*, **37**, 750, 1941.
23. WECHSLER, I. S.: *Original Source of Déjérine's Syndrome, A Textbook of Clinical Neurology*, Philadelphia and London, Saunders, 1928.
24. WELCH, W. H., and ROLLESTON, H. D.: *Embolism and Thrombosis, System of Medicine* (London), MacMillan, **6**, 691, 1909.
25. WHEELER, E. G.: *Canad. Med. Assn. J.*, **11**, 532, 1921.

IMPORTANCE OF URINARY CHLORIDE DETERMINATIONS IN TREATMENT OF PATIENTS HAVING PYLORIC OBSTRUCTION*

A REVIEW OF 50 CASES OF DUODENAL ULCER

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THE importance of fluid and mineral salt balance in patients having gastric retention due to duodenal ulcer is well recognized. However, the need for administering sodium chloride is commonly based on plasma chloride determinations. Haden^{6,7} pointed out that the plasma chloride content is preserved at the expense of the tissue chloride so that the amount of chloride in the blood may be normal when the tissue chlorides are depleted. Therefore, the true status of chloride deficiency would not be indicated by plasma chloride alone.

As a result of Haden and Orr's⁸ experimental work 20 years ago, urinary chloride determinations have been used routinely at this clinic with gratifying results as a basis for the sodium chloride needs of patients. The purpose of this review is to present further evidence, derived especially from study of 50 patients with duodenal ulcer, that urinary chloride determinations furnish more accurate indications for sodium chloride therapy than do plasma chloride determinations. Twenty patients did not have true pyloric obstruction due to cicatricial narrowing, since the obstruction was relieved by medical management. The remaining 30 patients were operated upon.

The shortest period of medical management was 3 days, the longest 9 days, and the average 5 days. The details were similar to those reported by Collins and Rossmiller.² In addition to restoring fluid and electrolyte balance, either single nightly gastric aspiration or Wangensteen drainage during part of each 24-hour

period was included. Fluid and sodium chloride balance was not considered to be present until the patient was excreting in a 24-hour period at least 1500 cc. of urine having a normal specific gravity and containing at least 5 gm. of sodium chloride. Operation was not undertaken until these conditions were established.

Methods. Plasma Chlorides. The Osterberg modification of the Whitehorn method¹² was used for determination of plasma chlorides. We consider that the normal values for this method are 520 to 595 mg. per 100 ml.

Urinary Chlorides. The Volhard-Hardy procedure¹⁰ was used for the determination of urinary chlorides. Chloride values in the urine are measured in terms of sodium chloride. The normal 24-hour urinary chloride excretion value is 5 to 10 gm.

When the usual laboratory facilities are not available, urinary chloride determinations are easily made using the simple procedure described by Fantus.⁴ To 10 drops of urine in a test tube add 1 drop of a 1 to 5% potassium chromate solution. The fluid will assume a distinctly yellow color. With the same dropper, or one of the same caliber, add drop by drop a 2.9% silver nitrate solution until a permanent and distinct color change to red-brown occurs, resulting from the formation of silver chromate. The number of drops required to produce the change of color expresses in grams per liter the chloride content of urine.

Administration of Parenteral Fluids. As patients with obstruction at the pylorus require fluid therapy in the correction of fluid and electrolyte balance, the method of administration is important. Haden empha-

*. Awarded the William E. Lower Fellowship Thesis Prize for 1945.

sized the fact that in the absence of renal or cardiac failure the simplest measure of the completeness of therapy is the amount of sodium chloride being excreted by the kidneys. Surprisingly large amounts of sodium chloride are usually necessary, as much as 1 gm. per kilo of body weight, or 70 gm. for an average man of 154 pounds. If given in the form of physiologic sodium chloride solution (0.85%), about 80 liters would be required, which obviously would overtax the cardiovascular system. Therefore, 500 cc. of 3% sodium chloride solution is given intravenously at the rate of 40 to 60 drops a minute once or twice daily at the start of treatment. After the first 24 hours its administration is guided by urinary chloride determinations.

Haden⁶ described the usual course. The urinary excretion of chlorides changes little for a few days, and the blood chloride level, if not low at the beginning, remains much the same. The chloride is evidently being absorbed by the tissues, and when the need of the tissues is satisfied, often a large amount (5 gm. or more) is excreted. This is the proper time for operation from the standpoint of body chemistry. After operation the secretion of chlorides again decreases but not to such a low level as was present on admission. When the reaction to the operation has ceased, usually a large amount of chloride is again excreted. This is similar to the increased excretion after the crisis in lobar pneumonia. Chloride retention by the tissues may be a protective mechanism, since patients following such a course have fewer toxic symptoms than when the supply of chlorides is inadequate. The aim is to keep the urinary chloride excretion above 5 gm. in a 24-hour period.

Since additional fluid and food are usually required by these individuals, one or two additional intravenous injections of 1000 cc. of 5% glucose in 1% sodium chloride solution may be given daily by the slow drip method at the start of treatment. If severe dehydration is present, 1800 cc. of 3% glucose in 1% sodium chloride is given subcutaneously daily un-

til the fluid and mineral salt balance is reestablished.

Analysis of Clinical Data. In this series of 50 cases (Tables 1, 2) of duodenal ulcer complicated by gastric retention at the time of the initial examination, 41 patients were men and 9 women. The ages ranged from 20 to 81 years. Operations were performed on 30 patients. Eight patients had partial obstruction for less than 1 year, and the remaining 42 complained of intermittent attacks of at least partial obstruction from 2 to 35 years. Gastric retention disappeared under medical management in all except 3 patients in whom pyloric obstruction was not relieved. Operation was considered advisable because of the previous history of pyloric obstruction or the presence of a persisting narrow duodenal channel as shown by progress roentgen examinations. Five patients had gastric resection and 25 gastroenterostomy. The remaining 20 patients received only medical management, which was directed towards correcting dehydration, restoring chemical balance, and relieving the obstruction. Gastric aspiration and lavage was carried out nightly until the obstruction was relieved or operation was performed.

At the beginning of treatment plasma chloride determinations were made on 48 patients. In 27 the initial plasma chloride values were above 520 mg. per 100 ml., in 13 the range was from 510 to 520 mg., and in only 8 were the values less than 510 mg. of 34 patients having CO₂ combining power determinations, in 13 the values showed alkalosis, the highest being 86.2. In 7 the values showed an acidosis, the lowest being 17.6. Blood urea determinations were done on 46 patients. In 29 the values showed a high blood urea, the highest being 201 mg. per 100 ml. Plasma protein studies done in a few cases were found to be within normal limits.

Initially all the patients had low urinary chloride values. The 24-hour urinary output was carefully measured, and only 8 patients excreted more than 1500 cc.

Roentgen examination showed that

TABLE 1.—ANALYSIS OF 30 PATIENTS HAVING PYLORIC OBSTRUCTION TREATED BY SURGERY

Case	History	Age	Sex	Duration of symptom	Duration of last attack	No. of previous attacks	Plasma chlorides	Blood urea	CO ₂	Initial urinary chlorides, gm.	24 hr. urine, cc.	Röntgen rays, % retention/hr.	Total and fraction plasma proteins	No. of days medical treatment	Gastric aspirations	Total NaCl given, gm.	Final 24 hr. urinary chlorides, gm.	Final urinary output, cc.	Final plasma chlorides	Final blood urea	Final CO ₂	Final blood proteins	Final Röntgen rays, % retention/hr.	Period of medical treatment	Surgical intervention	
1	364,215	58	M	6 yrs.	2-3 wks.	Several	511	72	86.2	0.48	600	100/4	3.5/0.5	2.9	9	8	275	12.4	2500	544	33	65.3	7.0/3.8	3.2	11 days	G.E.*
2	337,695	52	M	1 yr.	1 mo.	1-2	528	42	53.8	2.5	670	50/4½	...	5	5	110	16.6	1760	561	33	62.0	6.2/4.3	1.9	16 days	G.E.	
3	386,932	50	M	5 mos.	2 wks.	Several	495	48	63.3	2.9	750	70/4½	...	5	5	150	10.5	2500	594	36	51.9	6.1/3.8	2.3	10 days	G.E.	
4	331,112	37	M	1 yr.	20 days	2	423	54	76.7	0.25	830	100/4	...	6	4	165	36.0	3560	..	27	57.6	7.8/5.6	2.1	Well for	G.E.	
5	344,266	30	M	10 yrs	7 days	Several	528	57	59.5	0.9	675	100/4½	...	5	4	100	9.3	1580	577	48	56.7	3 yrs.	G.E.	
6	354,619	32	M	5 yrs.	1 mo.	Several	528	201	86.2	2.5	700	95/4	6.9/4.7	2.2	4	3	145	11.0	1460	..	33	60.5	8.7/6.5	2.2	2 yrs.	G.E.
7	364,216	58	M	18 yrs.	10 days	Several	511	72	67.2	0.48	600	100/4	...	10	9	245	5.0	1750	544	51	65.3	10 days	G.E.	
8	341,287	70	M	30 yrs.	1 yr.	Several	528	48	50.0	2.7	1000	60/4	...	5	3	80	6.9	1355	..	36	..	7.4/5.9	1.5	10 days	G.E.	
9	343,165	42	F	5 yrs.	4 wks.	Several	544	45	52.8	1.9	890	80/4½	...	7	4	120	13.0	2080	528	30	59.0	10 days	G.E.	
10	371,296	40	M	17 yrs.	6 mos.	1-2	495	45	17.6	0.9	1100	80/4½	...	5	4	125	4.2	715	544	..	49.0	10 days	G.E.	
11	337,117	42	M	2 yrs.	2-4 mos.	Several	511	57	..	1.7	650	60/4	...	5	5	120	13.2	2060	577	27	10 days	G.E.	
12	336,213	76	M	15 yrs.	1 yr.	Periodic	462	111	..	0.18	260	85/5	...	5	4	140	14.6	2400	528	51	8 days	G.E.	
13	386,294	38	M	1 yr.	Few wks.	2	561	42	59.5	0.40	510	95/4½	...	6	5	150	19.2	1940	Well for	G.E.	
14	353,128	69	M	5 yrs.	2 mos.	4-6 wks.	511	60	..	0.80	500	100/4	...	5	4	150	18.2	2500	4 yrs.	G.E.	
15	341,188	34	M	10 yrs.	2 wks.	2	512	50	38.2	2.4	660	50/4½	...	6	3	120	5.7	570	..	57	10 days	G.E.	
16	366,599	29	M	3 yrs.	4-5 wks.	1	544	36	..	0.5	500	50/4½	...	5	2	150	7.9	850	5 mos.	G.R.†	
17	346,665	50	M	1 yr.	2 mos.	1	528	..	1.5	380	80/5	4	3	95	16.5	2300	6 days	G.E.	
18	360,795	55	M	5 yrs.	4 days	4-5	511	42	..	0.35	350	50/4½	...	6	5	175	14.2	2875	511	33	8 days	G.E.	
19	374,059	54	M	7 yrs.	7 days	6	495	72	53.8	1.1	450	100/4	...	6	5	150	13.9	2385	..	45	4 mos.	G.E.	
20	341,188	42	M	18 yrs.	1 wk.	Several	511	30	..	1.4	710	90/4	...	4	4	152	8.4	2080	7 days	G.E.	
21	388,581	52	M	25 yrs.	5 days	Several	..	30	..	0.9	640	80/4½	4.5	4	2	60	7.8	650	9 days	G.R.	
22	375,528	50	M	3 yrs.	Few wks.	Several	..	42	..	1.3	3850	90/4	...	6	5	251	15.2	1525	19 days	G.R.	
23	391,998	64	M	15 yrs.	2 mos.	1	561	57	69.1	1.2	1275	100/4	...	7	7	175	4.4	1350	561	30	51.9	14 days	G.E.	
24	392,958	45	M	8 yrs.	8 days	Several	544	39	53.8	0.3	900	100/4	...	4	4	125	11.6	2100	571	35	51.8	30 days	G.E.	
25	308,297	65	F	3 yrs.	2 wks.	2	561	27	53.8	0.8	400	95/24	...	9	8	280	10.9	2100	G.R.	
26	310,627	36	F	2 yrs.	3 wks.	2	478	60	..	0.15	370	90/4	...	7	7	125	13.9	1580	14 days	G.E.	
27	320,803	48	M	20 yrs.	1 yr.	3	528	45	62.5	1.5	460	90/4½	...	4	4	100	5.6	800	528	30	62.6	8 days	G.E.	
28	330,128	58	M	4 mos.	2 wks.	1	561	51	48.1	1.4	900	65/4½	...	4	4	60	11.3	1170	511	54	59.6	6 days	G.E.	
29	331,815	50	M	16 yrs.	2 mos.	Several	561	42	47.1	0.2	800	80/4½	...	4	4	60	7.5	2400	5 days	G.E.	
30	318,738	57	M	12 yrs.	1 wk.	Several	495	51	65.3	1.25	625	60/4½	...	4	4	60	6.8	800	526	42	52.6	6 8/4.8	2.0	20 days	G.R.	

* G.E. = Gastroenterostomy. † G.R. = Gastric resection.

TABLE 2.—ANALYSIS OF 20 PATIENTS HAVING PYLORIC OBSTRUCTION TREATED BY MEDICAL MANAGEMENT

Case	History	Age	Sex	Duration of symptoms	Duration of last attack	No. of previous attacks	Plasma chlorides	Blood urea	CO ₂	Initial urinary chlorides, gm.	24 hr. urine, cc.	Röntgen rays, % re- tention/hr.	Total and fraction plasma proteins	No. of days medical treatment	Gastric aspirations	Total NaCl given, gm.	Final 24 hr. urinary chlorides, gm.	Final urinary output, cc.	Final plasma chlorides	Final blood urea	Final CO ₂	Final blood protein			Final Röntgen rays, % retention/hr.	Last note
31	374,112	64	F	7 yrs.	2 wks.	Several	528	105	38.5	0.9	605	65/3	6.3/4.1	2.2	4	3	70	13.7	3000	511	30	58.5	6.3/3.7	2.6	In 24 days none/4½	1942
32	357,191	81	M	35 yrs.	8 days	Several	528	69	35.7	1.18	1980	65/4½	...	3	3	85	10.9	2210	..	54	In 13 days none/4½	1941	
33	308,100	52	M	30 yrs.	14 days	2	528	54	..	0.7	1400	100/4½	...	7	6	120	9.4	4000	541	30	In 7 days none/4½	1943	
34	414,321	58	M	3 yrs.	2 wks.	Several	412	108	71.0	0.2	700	100/4½	...	8	7	200	18.0	4000	561	30	57.6	In 1 mo. none/4½	1944	
35	339,715	54	M	5 yrs.	2 mos.	1	526	52	52.6	0.18	696	30/4½	...	4	2	60	16.8	2600	511	30	In 11 days none/4½	1940	
36	350,163	49	M	2 yrs.	2 wks.	1	511	60	..	1.10	400	75/4½	...	7	4	150	9.1	1800	528	24	In 11 days none/4½	1941	
37	350,508	54	F	15 mos.	2 wks.	1	511	60	42.2	0.4	310	70/4½	...	4	4	100	17.6	2770	561	39	50.0	In 10 days none/4½	1941	
38	389,742	50	M	7 yrs.	4 mos.	1	545	33	60.5	0.7	800	100/4½	...	4	3	75	6.7	2000	528	30	52.5	In 10 days none/4½	1943	
39	415,420	52	M	35 yrs.	2 wks.	Several	511	30	..	0.7	1400	100/5	...	5	5	125	9.4	4000	544	33	..	6.5	...	In 6 days none/3	1944	
40	336,954	34	F	1 yr.	7 days	1	511	24	66.2	1.5	1590	69/4½	...	7	6	150	11.0	2200	540	28	59.2	In 9 days none/4½	1940	
41	339,562	20	F	1 yr.	Mos.?	1	561	0.57	2370	60/4½	...	6	2	150	6.4	2100	528	In 14 days none/4½	1940	
42	339,557	68	M	3 yrs.	1 mo.	1	511	48	..	0.6	740	80/5	...	6	3	130	10.3	1300	In 15 days none/4	1940	
43	300,478	36	M	7 yrs.	1 yr.	Several	544	39	44.3	0.7	2840	30/5	...	7	4	175	12.4	1480	544	30	56.7	10/3	1940	
44	407,795	60	M	1 yr.	4 days	1	500	39	52.2	2.4	2000	35/24	...	9	9	245	9.8	2600	..	36	48.1	1/6	1941	
45	314,304	63	F	10 yrs.	3 mos.	Several	594	60	50.1	0.53	400	25/4½	...	5	5	125	10.5	1825	Nonh/4½	1942	
46	341,168	39	M	3 yrs.	2 wks.	1	561	0.93	1340	80/5	...	6	2	120	5.7	570	In 8 days none/4½	1944	
47	110,952	64	M	10 yrs.	1 mo.	Several	544	27	57.0	2.0	1000	100/4	...	5	5	140	8.8	2950	511	none/6	1941	
48	280,178	71	M	8 yrs.	4 days	2	561	45	69.1	0.29	200	90/6	...	8	8	226	9.2	2000	528	30	52.8	None/3½	1944	
49	165,115	48	F	1 yr.	2 wks.	1	528	27	61.4	0.82	800	100/6	...	5	6	65	7.6	2600	577	27	45.3	None/7	1944	
50	395,985	35	M	3 yrs.	7 days	1	528	24	61.4	0.8	600	60/24	...	5	4	75	8.2	2200	514	24	52.4	None/3½	1943	

after $4\frac{1}{2}$ hours 48 patients had more than 50% retention, and 2 had 25 to 50% retention.

Medical management varied somewhat for each patient. Some did not seem to be particularly dehydrated, but urinary chloride values were extremely low as compared with accepted normal values. These patients were given 15 to 35 gm. of sodium chloride parenterally daily, 500 cc. of 3% saline intravenously in the morning, and 1000 cc. of 5% glucose in 1% saline in the afternoon by slow drip method. This was done to restore the chloride balance as rapidly as possible without overburdening the circulatory system. Patients in whom dehydration was as important as salt depletion were given 1800 cc. of 3% glucose in 1% saline subcutaneously and 1000 to 2000 cc. 5% glucose in 1% saline intravenously daily.

The daily urinary excretion value was used as an index of treatment in restoring the chloride balance. The excretion level was always low at first, and subnormal levels persisted during the first few days of treatment. Then suddenly *regardless of the plasma chloride levels*, normal or high, chlorides were excreted in the urine. This seemed to indicate that chloride balance had been restored and that *the tissues had adequate chlorides.*

Normal chloride balance was restored in 3 to 9 days, the average being 5.

Initially all of the patients had low urinary chloride values. Forty patients had a plasma chloride value of 510 mg. per 100 ml. or higher. These patients required approximately the same amount of sodium chloride to bring the urinary chloride excretion values to normal as did 8 patients whose plasma chlorides were definitely lower. The important factor is that patients who received an average of 120 gm. of sodium chloride for approximately 5 days excreted during this period an average of about 20 gm. in the urine and another 20 gm. in the gastric secretion. This left a net total of about 80 gm. of retained sodium chloride; this could be

considered the amount necessary to restore chloride balance.

Obviously, if plasma chloride values had been used as an index of treatment, *only 8 patients in this group would have received an adequate amount of sodium chloride.* Consequently, the 40 patients with plasma chloride values of 510 mg. per 100 ml. or higher would probably not have received any sodium chloride.

After treatment 10 patients excreted less than 1500 cc. of urine daily. This is explained on the basis of normal kidney function and high concentrated urine. With a small amount of fluid the kidney, because of its concentration power, excreted more salt in the urine.

All plasma chloride values were normal after the treatment. Both the alteration in total non-protein nitrogen content of the blood and the disturbance of the acid-base balance at the beginning of treatment returned to normal after the chloride balance had been restored.

Roentgen examination showed that in 36 patients the obstruction was completely relieved. Four had minimum retention, and 10 did not have further roentgen examination because operation was performed immediately after restoring chemical balance. There was no gastric retention 2 days before operation in 7 of these 10 patients. In the remaining 3 patients the pyloric obstruction was not relieved by medical management.

From a review of the 50 cases it is obvious that regardless of the age of the patient or the history of previous pyloric episodes, *a 5-day trial of adequate medical management is required in order to know the degree of cicatricial stenosis of the pylorus.* In 20 patients in whom pyloric obstruction was caused by spasm or inflammatory edema, medical management proved satisfactory.

Discussion. 1. *Hypochloremia.* There are several approaches to the problem of salt replacement in patients with high intestinal obstruction. In the past the method of trial and error was used by the clinician, who, after determining the

plasma chloride concentration, gave the amount of salt he supposed the patient needed. To see how accurately he had estimated the patient's requirements, he again determined the plasma chloride level.

This method has several faults: (1) If the plasma chloride concentration is determined too soon after saline administration, misleading values will be obtained. (2) If the salt need of the patient is underestimated, valuable time will be lost. (3) Excessive salt administration will not be shown by an abnormally high plasma chloride level, because the excess is excreted in the urine. Often in sick patients, as shown in several of the patients presented, the level cannot be raised to the lower limits of normal. In these, if the clinician uses only the plasma chloride level as an index of overdosage of salt, he is likely to be misled into forcing salt upon patients unable to attain a normal plasma chloride level at the time.

Bartlett, Bingham, and Peterson¹ showed that hypochloremia could be prevented by replacing abnormal fluid losses with equal volumes of physiologic saline solution, the amount of which was determined by means of a formula, which will be explained later. When losses were replaced with an equal volume of Ringer's solution, a fairly satisfactory plasma chloride level was obtained. However, the daily urinary excretion of salt fell below normal, indicating that an insufficient amount of salt had been administered.

The use of the volume for volume rule makes it necessary that the patient be under the physician's care when loss of body salt is initiated. Many times the patient loses an unknown amount of salt-containing fluid before consulting a physician, and therefore the volume for volume rule cannot be applied.

Based on the assumption that the plasma chloride level is a satisfactory index of chloride concentration in the body, Bartlett, Bingham, and Peterson¹ developed a formula referred to previously for calculating the salt requirement of patients with hypochloremia. According

to their formula it may be assumed that approximately 20% of body chloride has been lost when the plasma chloride level is 20% below normal. When the normal salt content of the body (0.248% of body weight) and the lost portion of salt, as indicated by the plasma chloride level, are known, the number of grams of salt needed to restore chlorides to normal is calculated as follows:

$$\begin{aligned} \text{Normal} &= \\ \text{Normal plasma chloride} - \text{actual plasma chloride} \\ &= \frac{0.0248 \times \text{body weight (gm.)}}{\text{Normal plasma chloride}} \end{aligned}$$

For clinical purposes this formula was somewhat cumbersome, and a simpler rule was made. The patient will receive 0.5 gm. of salt per kg. of body weight for each 100 mg. required to raise the plasma chloride level to normal.

However, in using this clinical rule certain complicating factors must be considered: (1) The plasma chloride content is preserved at the expense of the tissue chloride, so that the amount of chloride in the blood may be normal, while the tissue chlorides are depleted. In such cases chloride deficiency is not indicated by plasma chloride values alone. (2) If a patient's dehydrated weight is used in calculating his salt requirements, less salt will be given than if his hydrated weight is used. (3) Dehydration tends to concentrate the blood, which in turn raises the plasma chloride level. If the salt needs are calculated on the basis of this plasma chloride level, the amount of salt given will be less than if the levels are calculated when the blood is not concentrated. (4) If sodium and chloride ions are lost in equal proportions, or if sodium ions are lost in excess of chloride ions, a certain amount of water is also eliminated in the effort to keep the sodium concentration and the osmotic pressure of the body fluids constant. Under these circumstances the plasma chloride concentration may be normal, although loss of sodium and chloride is significant. Thus the plasma chloride level does not accurately indicate the salt needs of the body.

In attempting to calculate the need for chlorides by plasma chloride determinations the following difficulties and inaccuracies are apparent: (1) Salt loss cannot be replaced by the volume for volume rule because it cannot be accurately measured. (2) The formula and clinical rule depend upon factors which are quite variable. (3) Although the plasma chloride level can be determined at frequent intervals and salt given as indicated, this method does not invariably insure the maintenance of an adequate salt balance because plasma chloride values are not always a true indication of the salt requirements.

On the other hand, *urinary chloride determinations are simple and give the most accurate indication of chloride needs.* As long as the patient excretes from 5 to 10 gm. of salt a day in the urine, there is no danger of tissue salt depletion. It is well known that after a few days of deficient salt intake, the kidneys show a remarkable ability to conserve the salt remaining in the body, and the urinary salt excretion drops to less than 0.5 gm. a day. Throughout this period there may be no significant alteration in plasma chloride concentration. Sometimes the body loses salt by an abnormal route, the plasma chlorides drop below normal, and the salt content of the urine generally becomes less than 1 gm. per day. When salt is given in excess of tissue needs, large amounts of salt are excreted in the urine. Gamble⁵ pointed out that if water and sodium chloride are abundantly supplied, normal kidneys will correct the acid-base balance of the plasma by excreting the ion not needed by the body. As shown by Haden and Orr,⁹ chlorides other than sodium chloride are unsatisfactory for correction of hypochloremia. Therefore, urinary chloride determination is more practical for ascertaining the correct salt balance of the body.

2. Disturbance of the Acid-base Balance. Diminution in plasma chloride concentration with its attendant alteration of electrolyte distribution and acid-base bal-

ance is one of the most significant metabolic features of pyloric obstruction.

Loss of excessive quantities of water from the body is associated with the consequent loss of proportional amounts of electrolytes, because the body fluid concentration must be maintained within narrow limits. In dehydration due to excessive vomiting large quantities of hydrochloric acid are lost from the stomach. As a result of the loss of Cl ions from the blood, an excess of base, chiefly sodium, is retained in the form of bicarbonate. In this way neutral salt (NaCl) is replaced by an alkaline salt (NaHCO₃), which results in alkalosis. *Thirteen cases in this series corroborate this statement.*

The inanition and carbohydrate deficiency which accompany continued vomiting may contribute to the production of alkali deficit because of associated starvation ketosis. The liver preferentially burns carbohydrate, but in its absence fat and protein are oxidized at excessive rates. When this occurs, ketone bodies and glucose as end products of fatty and amino acid oxidation in the liver are liberated into the blood stream and utilized by extrahepatic tissues. However, the rate of production may exceed that of utilization, and an accumulation occur in the blood and give rise to ketosis.

In 7 of our cases there was little hydrochloric acid in the gastric juice. Continuous vomiting produced dehydration, which resulted in acidosis demonstrated by a fall in the CO₂ combining power. Maybe the ketone acids resulting from starvation in the pyloric obstruction partly offset the bicarbonate increase produced by loss of chloride.

3. Increase in Non-protein Nitrogen Constituents or urea of the whole blood. Alteration in the blood urea content of the blood in 29 cases of pyloric obstruction was due to two factors: (1) Excessive vomiting and consequent dehydration make a minimum amount of body fluid available for renal excretion. Since a certain dilution is necessary for their elimination, nitrogenous substances of the blood

are retained in proportion to the degree of oliguria, which sometimes is extreme. (2) Dehydration due to water privation (vomiting and gastric lavage) after 42 hours and starvation alter and increase the rate of protein metabolism, which results in catabolism. This is commonly regarded as toxic destruction of protein. The increase in the level of blood urea, which occurs under such circumstances, is due to the *combined effects of catabolism and dehydration*.

Safety Factors. Cutting, Lands, and Larson³ concluded that cats could tolerate the rapid intravenous administration of large amounts of sodium chloride solution if the solution was not more concentrated than 2%. The lethal amount is approximately 500 cc. of 1% solution per kg. of body weight when the injection is made at approximately 5 cc. per kg. of body weight a minute. Translated into terms of a human being weighing 70 kg., or 154 pounds, this amounts to a total of 35 liters of 1% solution given at the rate of 350 cc. a minute. The quantity of fluid and speed of injection is greater than that used in clinical practice. Within 24 hours of administration of this large infusion of 1% sodium chloride, about 80% of the water and almost all the salt were eliminated by the kidneys. Indeed in almost half of the animals more sodium chloride than was injected was excreted.

In a series of patients Milbert¹¹ used hypertonic solutions (5% sodium chloride, 10% glucose, and so forth) at the rate from 57 to 106 cc. a minute, which exceeded the accepted limits of safety.

Hypertonic saline solution (3% sodium chloride) was used routinely in our cases. The slow drip method was used, 40 to 60 drops per minute. Urinary chloride excretion and output of urine were checked daily. The urinary chloride values were less than 5 gm. daily at the start of treatment, regardless of administration of 15 to 35 gm. of salt. The quantity of urine excreted was less than 1500 cc. in 45 cases. Both output of urine and urinary chloride values were increased gradually until

normal values were acquired at the end of the treatment (average 5 days).

Therefore, 3% sodium chloride is not contraindicated because of its hypertonicity. The results obtained in these cases show that an adequate salt balance can be obtained in an average of 5 days, when urinary chloride excretion value is used as an index of treatment.

Summary and Conclusions. 1. For the accurate appraisal of chloride balance in 50 cases of duodenal ulcer with obstruction, the plasma chloride determinations were found to be less reliable than the more simply performed urinary chloride determinations.

2. In 80% of the cases there was marked diminution in urinary chlorides, although plasma chlorides were normal at the time of the initial examinations. This resulted from depletion of tissue chlorides, which maintained a normal level in the blood.

3. In 60% of the cases there was severe alteration in the acid-base balance of the blood. Forty per cent had alkalosis and 20% acidosis.

4. Azotemia was present in more than 60% of the cases.

5. Hypochloruria together with nitrogen retention and disturbances in the acid-base balance constitutes the outstanding biochemical feature in patients having pyloric obstruction.

6. In patients with pyloric obstruction the necessity for supplying sodium chloride and water is well established.

7. In administering large amounts of salt 3% saline solution is preferred. The quantities of salt needed are indicated by urinary chloride determination.

8. Acid-base balance and chloride balance with normal values of blood urea were obtained after a period of approximately 5 days. During this period adequate amounts of water and sodium chloride were administered.

9. Twenty patients were relieved of pyloric obstruction by medical treatment alone. Thirty patients were treated surgically after the acid-base balance was restored by medical treatment. The proper

time for surgical intervention from the normal urinary chloride excretion (more chemical standpoint was determined by a than 5 gm. in 24 hours).

REFERENCES

1. BARTLETT, R. M., BINGHAM, D. L., and PETERSON, S.: Salt Balance in Surgical Patients, *Surgery*, **4**, 441, 1938; 614, 1938.
2. COLLINS, E. N., and ROSSMILLER, H. R.: Obstruction Symptoms *versus* Pyloric Obstruction; Importance of Medical Management, *S. Clin. North America*, **21**, 1495, 1941.
3. CUTTING, R. A., LANDS, A. M., and LARSEN, P. S.: Distribution and Excretion of Water and Chlorides After Massive Saline Infusion. An Experimental Study, *Arch. Surg.*, **36**, 586, 1928.
4. FANTUS, B.: Fluid Postoperatively, *J. Am. Med. Assn.*, **107**, 14, 1936.
5. GAMBLE, L.: Dehydration-extracellular Fluid—a Lecture Syllabus—Charts 36, 39, 42, 1942, *New England J. Med.*, **201**, 909, 1929.
6. HADEN, R. L.: Preparation of Patients for Operation on the Upper Gastro-intestinal Tract, *S. Clin. North America*, **21**, 1465, 1941.
7. HADEN, R. L.: Treatment of the Toxemia of Obstruction of the Gastro-intestinal Tract, *S. Clin. North America*, **17**, 1399, 1937.
8. HADEN, R. L., and ORR, T. R.: Chemical Changes in Blood After Pyloric Obstruction, *J. Exp. Med.*, **37**, 377, 1923; Chemical Changes in the Blood of Man After Acute Intestinal Obstruction, *Surg., Gynec. and Obst.*, **37**, 465, 1928; Chemical Changes in the Blood of the Dog After Pyloric Obstruction, *J. Exp. Med.*, **37**, 365, 1923; Chemical Factors in the Toxemia of Intestinal Obstruction, *J. Am. Med. Assn.*, **91**, 1529, 1928; Chemical Findings in the Blood of the Dog After Closed Loop-obstruction of the Jejunum, *J. Exp. Med.*, **49**, 955, 1929; Chemical Findings in the Blood of the Dog After Temporary Obstruction of the Pylorus, *J. Exp. Med.*, **48**, 591, 1928; Chloride Content of the Tissues of the Dog After Experimental Gastro-intestinal Tract Obstruction, *J. Exp. Med.*, **44**, 435, 1926; Distribution of Chlorides in the Blood of the Dog After Experimental Intestinal Obstruction, *J. Exp. Med.*, **41**, 113, 1925; Effect of Sodium Chloride on the Chemical Changes in the Blood of the Dog After Obstruction of the Cardiac End of the Stomach, *J. Exp. Med.*, **48**, 627, 1928; Experimental High Intestinal Obstruction in the Monkey, *J. Exp. Med.*, **41**, 107, 1925; Experimental High Jejunostomy in Intestinal Obstruction, *J. Am. Med. Assn.*, **87**, 632, 1926; Sodium Content of the Blood After Experimental Intestinal Obstruction, *J. Exp. Med.*, **41**, 119, 1925; Use of Sodium Chloride in Treatment of Intestinal Obstruction, *J. Am. Med. Assn.*, **52**, 1515, 1924.
9. HADEN, R. L., and ORR, T. R.: Effect of Inorganic Salts on the Chemical Changes in the Blood of the Dog After Obstruction of the Duodenum, *J. Exp. Med.*, **39**, 321, 1924.
10. KOLMER, J. A., and BOERNER, F.: *Approved Laboratory Technic*, 2d ed., New York, D. Appleton-Century Co., pp. 162-163, 1938.
11. MILBERT, A. A.: Infusion Reactions With Special Reference to "Speed Shock," *Am. J. Surg.*, **26**, 479, 1934.
12. OSTERBERG, A. E., and SCHMIDT, E. V.: Estimation of Plasma Chlorides, *J. Lab. and Clin. Med.*, **13**, 172, 1927.

ROENTGEN STUDIES OF THE SPLEEN

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THESE studies were carried out in an effort to arrive at an objective and more accurate method for determining the size of the spleen. Clinicians have long realized the limitations of physical examination in evaluating the size of this organ. Although it has long been a common practice to attempt to visualize the spleen by roentgen ray, no definite criteria have been established for interpreting the roentgen shadow.

It is realized by all physicians that some enlarged spleens are not palpable. This may be due to obesity, tense or well developed abdominal muscles, a narrow costal angle, or most often, a high diaphragm. On the other hand, it is not realized by many physicians that some palpable spleens are not enlarged. These spleens are often palpable only because of a lax abdominal wall, wide costal angle, malnutrition, or most frequently, a low diaphragm. Satisfactory roentgen criteria for spleen size will obviate many unnecessary and time-consuming diagnostic procedures in such instances.

Case Material. During the last 18 months, over 300 patients in an Army General Hospital have had roentgenograms made of their spleens. Most of the subjects were young men; 50% had palpable spleens or diseases which might cause splenic enlargement. The majority of this group had, or had had malaria. A moderate number of cases of cirrhosis of the liver, hepatitis, and infectious mononucleosis, and isolated cases of thrombocytopenic purpura, congenital hemolytic jaundice, leishmaniasis, sarcoidosis, Hodgkin's disease, leukemia, and so forth were studied. The remaining 50%, the control group, consisted of neuropsychiatric, general medical and surgical patients, with no indication of any disease which might cause splenic enlargement.

Technique. Postero-anterior films are taken before meals since a full stomach may interfere with visualization of the organ; no other preparation is employed. The plates are made in the PA projection, using the Potter-Bucky diaphragm, 100 milliamperes, with a time exposure of 0.5 second, at a target film distance of 36 inches. The kilovoltage varies with the thickness of the patient and averages 6 to 8 kv. less than the usual stomach technique. The central ray is directed through a point halfway between the midline and the left lateral chest wall, three finger breadths below the ensiform cartilage.

Interpretation. During this study, it became obvious that there was considerable variation in the size of normal spleens in different individuals, although the spleen size remains constant in a given individual. It appears, in general, that the size of the spleen varies with the size of the individual, although no definite relationship has been established. According to Gray's Textbook of Anatomy, the normal spleen in an adult is about 12 cm. in length, 7 cm. in breadth, and 3 to 4 cm. in thickness. Due to the oblique position of the spleen, the width of the roentgen shadow is a combination of the anatomical breadth and thickness. A spleen that is visible in both its length and width presents no problem in menstruation. It is rarely found, however, that the spleen is visible in its entire length, whereas it is always possible to determine its width. The width is measured at the broadest visible point of the shadow, which is usually just below the hilus. It is measured to the outer border of the spleen, when this is visible, or the internal surface of the ribs, when this border is not visible.

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The length of the spleen can be determined in only a small proportion of patients, due to inability to make the upper portion of the organ visible. It was found in those cases where the upper pole can be visualized, that there is no constant relationship of the position of the spleen to the diaphragm. Thus the diaphragm cannot be used as a point from which to measure length.

Any rotation of the spleen on its long axis will alter its width, whereas rotation on its horizontal axis will alter its length. In doubtful cases, films taken in the A.P. left oblique may be of value. When rotation decreases either of these diameters, there must be a corresponding increase in density. Density, therefore, must be taken into consideration in determining spleen size, and is measured by comparing the spleen with the lower half of the left kidney. The density is considered increased if greater than that of the normal kidney. There was no evidence of renal disease in any patient in this series.

Using this technique, the lower pole of the left kidney is nearly always visible, and often its entire contour can be seen. The measurements of the kidney, as given in the standard text mentioned above, are $11\frac{1}{2}$ cm. in length, 5 to $7\frac{1}{2}$ cm. in breadth and $2\frac{1}{2}$ to 3 cm. in thickness. The spleen and kidney, therefore, are of comparable size and the relationship of the size of the kidney to that of the spleen is the ideal method for determining splenic enlargement. In the majority of films, however, this criterion cannot be used because the complete contour of both organs cannot be seen. When the complete contours can be seen, any spleen which is more than 85% the size of the kidney is regarded as enlarged. (The reason for arbitrarily using 85% in this comparison is that the magnification of the kidney is greater than that of the spleen in this projection.)

Thus the factors of width, density, and comparison with kidney size are used to determine the size of the spleen. The length of the spleen is infrequently found to be of value because of inability to

visualize the upper pole. In obscure cases, artificial pneumoperitoneum might be used to more clearly outline the spleen, particularly the upper pole; the authors have had no experience with this method.

Criteria. Only the factors of width, density, and comparison with kidney were used to establish these criteria. The size of the normal spleen was determined through study of the large series of controls. Normal spleen roentgenograms are shown in Figure 1. All patients were carefully followed clinically and much time and effort were expended in studying the spleen shadows. The following criteria were established:

1. The spleen is not enlarged if it is: (a) not visualized; (b) less than 5 cm. in width; (c) less than 85% the size of the kidney.

2. The spleen is enlarged if it is: (a) more than 6 cm. in width; (b) more than 85% the size of the kidney.

It is at once apparent that spleens from 5 to 6 cm. in width are not included in these criteria. In such instances, density is the deciding factor. Spleens from 5 to 5.5 cm. in width are not enlarged if their density is normal, but are questionably enlarged if their density is increased. Spleens from 5.5 to 6 cm. in width are only questionably enlarged if their density is normal, but are definitely enlarged if their density is increased (Table 1).

Results. There were relatively few splenic shadows which fell into the questionable group. In the vast majority of cases, the size of the spleen could be definitely and readily determined from the roentgenogram.

In the majority of cases where the spleen was palpable, roentgen examinations showed splenic enlargement, using the above criteria. These included patients with malaria, infectious mononucleosis, cirrhosis of the liver, leishmaniasis, and congenital hemolytic icterus (Fig. 2).

In 17 instances where the spleen was palpable, roentgen examinations showed no splenic enlargement, and obviated extensive laboratory studies. These included

patients with psychiatric disorders and unexplained fever (Fig. 3). None of these patients were explored or autopsied, but the clinical course of each was compatible with the roentgen diagnosis.

culty can be surmounted only by taking films at frequent intervals. All of these men had very low diaphragms, with wide costal margins, rendering the spleen more readily palpable.

TABLE 1.—A SUMMARY OF CRITERIA USED

Interpretation	Width	Density
Normal	Less than 5 cm.	Normal or increased
	5 to 5.5 cm.	Normal
Questionably enlarged	5 to 5.5 cm.	Increased
	5.5 to 6 cm.	Normal
Enlarged	5.5 to 6 cm.	Increased
	More than 6 cm.	Normal or increased

Any spleen less than 85% the size of the kidney is not enlarged; any spleen more than 85% the size of the kidney is enlarged.

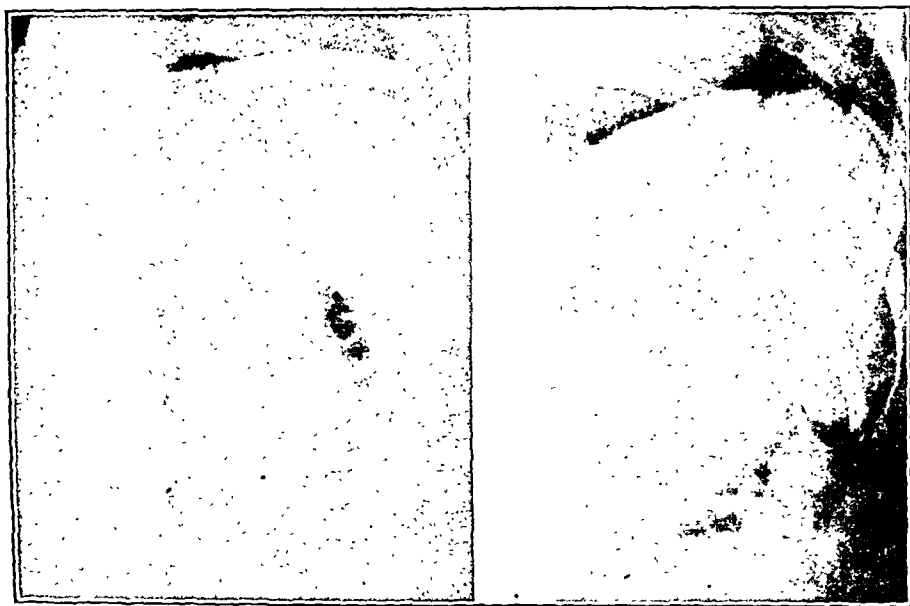


FIG. 1.—Normal splenic shadows in normal individuals. *Left*, less than 5 cm. in width. *Right*, less than 5.5 cm. in width, and not increased in density.

Five patients with a history of malaria did not have palpable spleens, and showed no enlargement of the spleen on the roentgenogram when they first came under observation. They later developed malaria, and a palpable spleen. The size of the spleen increased on the roentgenogram but was still within the normal limits established with the above criteria (Fig. 4). These patients evidently had very small normal spleens, which enlarged. It is quite possible that spleens which are not enlarged by our criteria, are indeed enlarged for that particular individual. This diffi-

Seven cases, 4 of malaria, 2 of cirrhosis of the liver, and 1 of thrombocytopenic purpura, did not have palpable spleens; but roentgen examination showed definite enlargement. The last of these underwent splenectomy, and the spleen was slightly enlarged, weighing 230 gr. after removal. It should be remembered that during delivery of the spleen at operation, a certain amount of blood may be squeezed out; so that this spleen may have weighed considerably more *in situ*. Three of the 4 patients with malaria developed palpable spleens when they developed clinical at-

tacks of malaria (Fig. 5). In the remaining 3 cases, the spleen could not be felt at any time.

Eight cases with normal sized spleens were studied to determine the effect of food, rest and moderate activity on the spleen size. Films were made shortly after

arising, 1 hour after breakfast, before mid-day dinner, and 2 hours after dinner. The patients carried on the normal activities of ambulatory hospital patients. These patients were also studied at weekly intervals for 1 to 3 months. No change in spleen size was found.

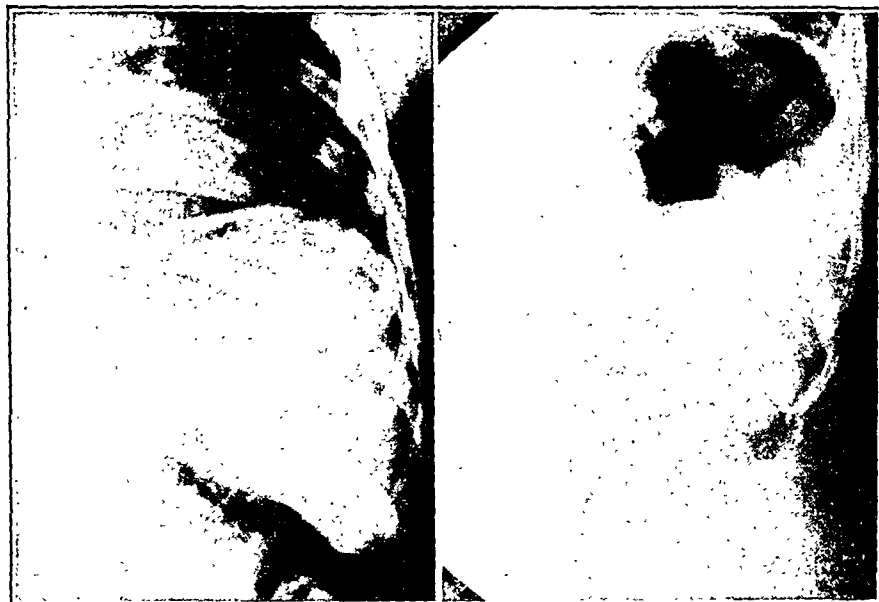


FIG. 2.—Enlarged palpable spleens. *Left*, 7.5 cm. in width (infectious mononucleosis). *Right*, 8 cm. in width (malaria).

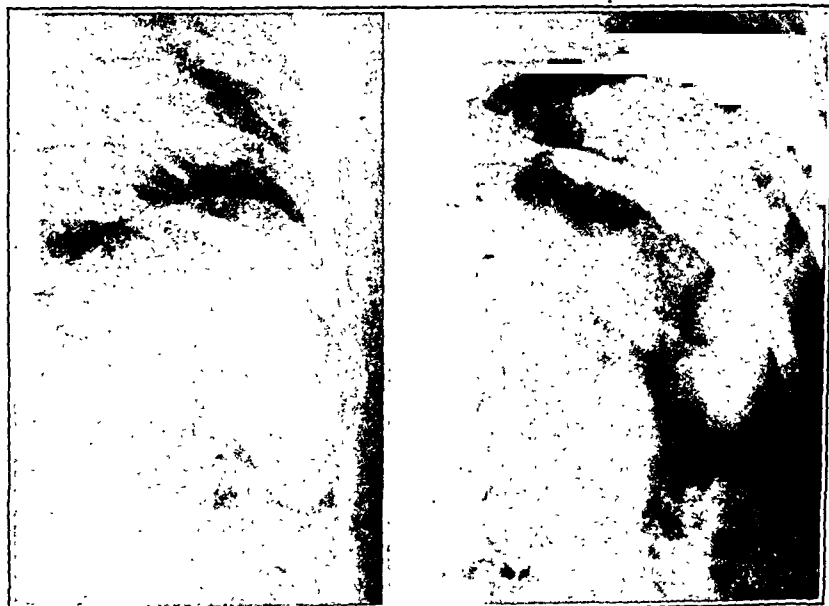


FIG. 3.—Normal patients illustrating palpable spleens which are not enlarged. Both spleens are less than 5 cm. in width.

Six cases with readily visible splenic shadows, who were recovering from recent attacks of tertian malaria, were studied before and after adrenalin. Films were made immediately before and 1, 5, and 15 minutes after the injection of 0.5 cc. of 1 to 1000 adrenalin subcutaneously. The

patients remained in the same position for all 4 films, and practice gave approximately the same position of the diaphragm in expiration. Four of the patients showed a marked decrease in spleen size, as illustrated in the accompanying diagrams (Fig. 6).

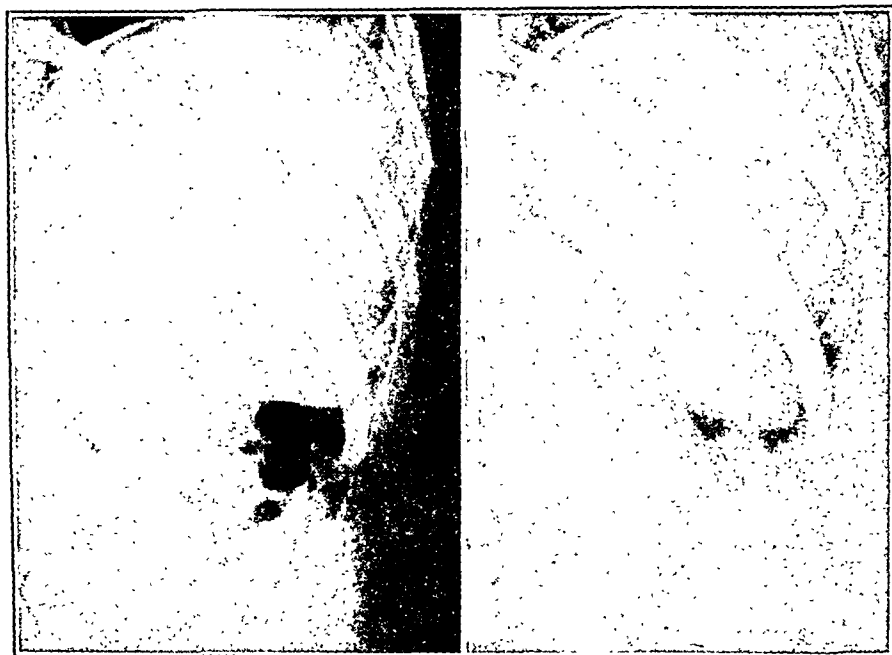


FIG. 4.—A spleen enlarged for an individual but still within normal limits by these criteria (see text). *Left*, less than 5 cm. in width. *Right*, 5 cm. in width, and of normal density.

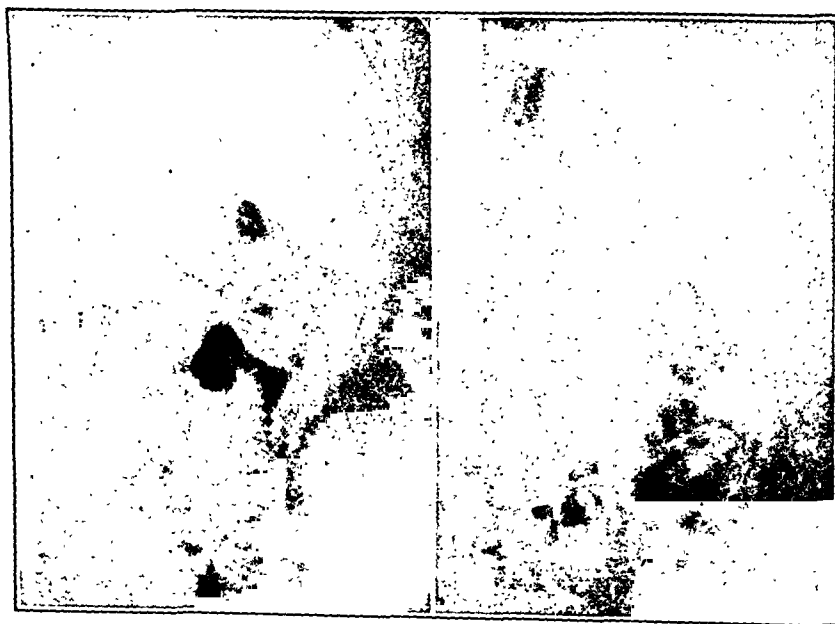


FIG. 5.—An enlarged spleen, *left*, which was not palpable. Five days later, *right*, during clinical malaria, spleen became larger and was palpable.

Summary. 1. A simple technique for roentgen examination of the spleen is described.

2. An attempt has been made to establish criteria for determining splenic enlargement.

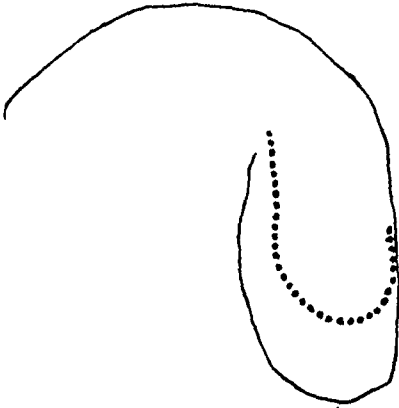


FIG. 6.—Composite tracings of spleen shadows, showing decrease in size after injection of adrenalin. — before injection of adrenalin. 15 minutes after injection of adrenalin.

3. These criteria depend upon the width, density, and relation to kidney size.

4. It is highly desirable that tables be worked out for determining the size of the normal spleen in relation to body height and weight.

5. There seems to be no diurnal variation in the size of the spleen, and no variation in relation to ingestion of food or moderate activity.

6. There is often a definite decrease in the size of the spleen, 5 to 15 minutes after subcutaneous injection of adrenalin.

Conclusions. 1. Roentgen examination of the spleen is a relatively simple, rapid, and inexpensive method that determines enlargement in the great majority of cases.

2. Many palpable spleens are not enlarged.

3. Many enlarged spleens are not palpable.

EMOTIONAL FACTORS IN OBESITY

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THE obese person has no desire to be told that he eats too much or that his organs are normal; instead he wishes to be told that he has a "gland trouble" and that he will have to take medicine to correct this. The physician often complies with his wishes and treats him with various substances, some harmful, while others do not harm particularly but are hardly more than placebos.

It is generally agreed that within limitations the laws of thermodynamics are applicable to the body and that obesity is due to "an over-all intake of energy which has exceeded the total dissipation of energy of the body, *i. e.*, a positive energy balance."⁸ Therefore, any form of therapy must consist of either a decrease in the energy intake or increase in the energy output. With rare exceptions it is not feasible to increase the energy output of an individual to the extent that obesity may be prevented or relieved. The therapy which should prove more efficacious and which should receive the attention of the patient and physician alike is the decrease in energy intake. Marked restriction of the caloric intake will alone cause a loss of weight, and the more accepted method of restricting the caloric intake is by giving the patient a calculated diet. Such diets may vary from 500 to 1500 calories. The experience in this and other clinics has shown that the incidence of failure is quite high when diet therapy is used alone.

Many observers^{1,2,5,8,10} have emphasized the fact that this desire for excessive food consumption is based on a disturbance in the psychologic make-up of an individual and that the stimulus is not derived from an abnormally functioning organ, but no reported studies can be found in which patients were treated by means of psycho-

therapy alone. This study was arranged to evaluate this form of therapy.

Materials. To obviate the economic and educational factors that are met with in an Out Patient Metabolism Clinic, it was decided to include in this study only the patients admitted to the Private Medical Clinic of Duke Hospital. All were under the direct supervision of the writer. The primary complaint was obesity or "nervousness" and frequently other complaints, such as hypertension, menopause, etc., were present. Complete physical examination and laboratory studies, including study of the blood and urine, basal metabolic rate, Roentgen ray of the skull, renal function, and electrocardiograms were made on the initial entrance to the hospital. Only those patients who were able to be up and attend to their duties were included in the study. All patients were 10 kg. or more over their calculated ideal body weight. Women in the menopause age were included. Patients with diseases commonly associated with obesity, such as given in Table 2, were not used in the experiment.

The weights were obtained by the same observer using the same balances for each determination, except in 6 instances when these data were supplied by the patient's home physician. On each return visit a blood pressure reading was obtained, the hemoglobin estimated, the basal metabolic rate determined and the urine examined, particularly for acid bodies.

A total of 93 patients were studied. These patients are divided into the following 4 groups:

Group 1. Thirty-eight patients were treated in the following manner: A detailed inquiry was made as to their developmental history, social and sexual adjustment, economic status, relationship to their family and friends and other factors that may have had influence on their

personality. An attempt was made at superficial psychotherapy which consisted of reassurance and interpretation. No calculated diet was given; however, an explanation of energy exchange and the caloric value of certain common foods was offered. Care was taken to explain the phenomenon of water retention in order to anticipate the periods during which no weight loss occurred. Instructions for keeping a food diary (measured) for 3 days previous to the clinic visit were given. No medication was prescribed in any instance.

Group 2. Thirty-five patients were given a calculated diet of 800 calories. An experienced dietician explained the diet to the patient and, when desired, on return visits further instructions were given by the dietitian. No medication was given and no effort at psychotherapy was attempted.

Group 3. Ten patients were given 5 mg. of amphetamine sulphate 3 times a day. No psychotherapy was attempted and no calculated diet was offered.

Group 4. Ten patients were handled as those in Group 3 except that thyroid substance was administered instead of amphetamine.

Results. In each of the 93 patients it was possible to demonstrate some emotional problem. For the most part, the type of psychoneurosis observed was varying degrees of tension state, characterized by afternoon occipital headache, vague gastro-intestinal symptoms, etc. Others had anxiety attacks, with excessive sweating, coldness of hands and feet, palpitation, etc. In some instances definite obsessive compulsive neurosis was observed. In the more severe emotional reactions the aid of a psychiatrist was obtained and in no instance was a patient with a psychosis treated. One of the most frequent precipitating factors during the past 4 years was worry over a member of the family in the armed services. No relationship was found to exist between the severity of the psychoneurosis and the weight of the patient.

An example of the less severe psycho-

neurosis is illustrated by the following patient:

O. M., a 28 year old white female, had maintained constant weight at 52 kg. since the age of 15 years. Her husband was inducted into the armed services and while stationed in this country there was no variation in the patient's weight. After her husband was sent on foreign service and had participated in several battles the patient developed the habit of eating between meals and at bedtime. Her weight increased 27 kg. in 8 months to 79 kg. The patient was seen in consultation at this time and an attempt was made to explain to her the reasons for her increased consumption of food. Her weight decreased 3.5 kg. in 4 weeks but did not progress beyond this level, however, until her husband was sent back to this country, she then lost weight down to 55 kg. where it has remained. Discussions were held with the patient relating to the caloric value of foods, but no calculated diet was offered.

A more severe type of reaction is illustrated in the following record:

C. K. G., a white, male merchant, aged 39 years, was admitted to Duke Hospital because of attacks of weakness that were associated with palpitation, sweating, fear of impending death and fear of crowds. He stated that he had always been highly excitable, given to worry over details which frequently resulted in marked insomnia. Three years previous to admission he was crossing the street at a crowded intersection when a car struck and seriously injured his small daughter. Immediately after this episode he experienced marked anorexia, nausea and vomiting. He refused food for 3 days, at the expiration of which time he was told that his child would recover completely. He then noticed that he would refuse to cross the street at the scene of the accident and in a short time began to dread crossing any street whether there was little or no traffic. At this time he developed anxiety attacks characterized by weakness, palpitation and sweating. These would occur immediately after crossing a street, and he found that if he ate something, usually a cold drink with crackers, he would experience immediate relief. When crossing the street, he had an impulse to throw himself in front of cars.

His total food intake increased to the point that, according to his food diary, it was estimated 3400 calories per day. In a period of 6 months his weight increased from a previously maintained level of 80 kg. to 102 kg. Upon admission to the hospital the physical examination, laboratory studies, including basal metabolic rate, Roentgen ray of the skull and chest, were normal. A psychiatric consultation was requested and psychotherapy was instituted. The patient was relieved of his attacks and the weight decreased to 85 kg. in 2 years, where it has remained. No calculated diet or medication was given.

All patients in Group 1 were followed for 1 year or more and 5 patients have been followed for 3 years. There was a total of 38 patients in this group, 28 females and 10 males. The youngest patient was 15 years of age, the oldest 78. Ten patients were between the ages of 30 and 40 years and 12 between the ages of 40 and 50 years. A family history of obesity was present in 14 instances.

Thirty-five patients showed weight loss in 2 weeks; in 1 instance a man weighing 181 kg. lost 6 kg. in this interval. The 3 patients who failed to lose weight in the initial period deserve more comment. One was a man 69 years of age who had been existing on a daily diet of 1 quart of whiskey, "vitamin pills," and meat for many years. He showed no interest in losing weight, and 1 year later had gained from 172.7 kg. to 175 kg. The other 2 patients were over 70 years of age and decided that they did not care to reduce their weight.

The immediate weight loss is of little importance unless the weight is maintained at the lower level. Arbitrarily, therefore, it was decided that unless a patient had maintained a weight loss of 5 kg. or more for 1 year, or if any relapses occurred after a year, the experiment was a failure. Of the 35 patients who showed prompt weight loss, 9 were considered failures by these criteria; indeed, 8 actually gained weight.

Twenty-one patients in this group had an elevation of the systolic blood pressure

above 160 mm. Hg. In 14 of the 21 patients the systolic pressure was lowered by 20 mm. Hg or more. The reduction of the blood pressure accompanied the initial weight loss during the first 6 months of the experiment. After this period there was a gradual rise of blood pressure in 12 of 14 patients, so that at the end of 18 months it had risen to the level observed initially. The diastolic pressure followed the same trend as did the systolic, but not to the same degree. In 2 patients the fall in blood pressure remained constant for 2 years or more.

The patients in Group 2, treated by diet alone, were used as controls. A total of 35 patients were followed for a year or more, 12 males and 23 females. The age groups compare roughly with those in Group 1; 1 patient was 16 years of age, 1 was 72, 12 were in the 30 to 40 year group, and 14 were from 40 to 50 years of age. A family history of obesity was present in 11 patients. All patients in this group lost weight varying from 1 to 3 kg. within the first 2 weeks but by the end of the first year there were 26 failures and 9 who had maintained the weight loss of 5 kg. or more. At the end of 2 years, 5 had not gained weight, 3 had gained to the initial weight, and 1 patient could not be located. Five patients lost 30 kg. or more with no deleterious effect upon their sense of well being or their general health.

Of the 9 patients whose treatment had been considered successful only 2 had hypertension and no appreciable effect was noted in either of them.

The patients in Group 3, who received 5 mg. of amphetamine sulphate 3 times a day, showed weight loss for the first 4 weeks; after this interval there was a slow gain back to the initial weight. This was true although the drug was continued and in 6 patients the dosage gradually increased to 10 mg. 3 times a day.

The patients receiving thyroid substance (Group 4) showed no appreciable weight loss until dietary measures were instituted. The amount of thyroid substance admin-

istered was sufficient in each instance to produce untoward symptoms.

A comparison of the 4 groups is summarized in Table 1.

Because of the frequent association of obesity with disease of the endocrine system and because of the reported experimental work on animals in which obesity occurred after producing lesions in the hypothalamus, the records of 88 patients, with a diagnosis of some endocrine disease, encephalitis or inactivity due to chronic illness, were examined. These results are given in Table 2. The 2 patients with hyperinsulinism had a gain in weight

genic factors bore a close relationship to the onset and development of obesity.

In experimental animals obesity has been produced by injury to the hypothalamus,⁷ but there is no proof that lesions in this area will produce obesity in man. Greene⁶ has analyzed a group of patients with diseases of the endocrine glands, suprasellar tumors and chronic encephalitis and has found that the incident of obesity in these conditions was little if any higher than patients with some other injury or disease that necessitated inactivity. An analysis of 88 patients in this clinic with a diagnosis of some endocrine

TABLE 1.—RESULTS WITH DIFFERENT TYPES OF THERAPY

	Total No. patients	Successful	Failures
Psychotherapy: No calculated diet	38	26	12
Calculated diet only	35	9	26
Amphetamine only	10	0	10
Thyroid substance only	10	0	10

TABLE 2.—RELATIONSHIP OF OBESITY TO ONSET OF VARIOUS MALADIES

	No. cases	Obesity present	Obesity antedating onset of illness
Myxedema	15	6	4
Cushing's syndrome	3	2	2
Hyperinsulinism	2	2	0
Pituitary tumors, including cysts	12	5	2
Menopause	30	20	18
Inactivity due to debilitating illness	10	6	2
Encephalitis (postinfectious)	16	4	0

of 17 and 24 kg. respectively. They had learned that an attack of unconsciousness could be prevented by eating food. In the other diseases listed, in most instances the onset of obesity antedated the diagnosis of the condition.

Discussion. While this study was not planned with the purpose of establishing a single etiology for the increased food consumption that characterizes the obese individual, it is believed that the results presented establish the fact that emotional tension and psychoneurosis will in certain people produce obesity. In no patient observed by the writer has the etiology proved to be other than an excessive desire for food, and in some instances a well defined phagomania was present. In all but 5 or 6 of a group of 50 patients studied by Schopbach and Matthews¹⁰ psycho-

disturbance, inactivity due to illness or encephalitis agrees with Greene's⁶ report. The fact that patients with encephalitis do not develop obesity does not necessarily argue against the theory that lesions of the hypothalamus will produce obesity since the lesions of encephalitis need not involve that part of the hypothalamus that affects the appetite.

The efficacy of the treatment outlined in this report, that is psychotherapy, cannot be denied. Danowski and Winkler⁴ reporting on the long term treatment of obesity by means of calculated diets only have reported that about 80% were failures. The number of failures in the control group reported here approximate those of Danowski and Winkler; however, the number of failures in the group that received psychotherapy alone were con-

siderably fewer. Gray⁵ has stated, "The treatment of obesity depends more on the mind than on the body." In the light of the material presented in this study we agree with the above statement.

As to the administration of drugs, it has been our experience that the patient is inclined to rely upon the drug rather than upon himself. His attitude is that so long as he takes a pill extra food will not affect his weight. Cutting³ has shown that amphetamine, propadrine hydrochloride and belladonna are of little aid in the control of obesity; however, he was more successful with thyroid substance than reported in this study. Pelner⁹ has advocated the use of amphetamine but emphasized that establishment of

proper good habits is necessary before maintenance weight loss is produced.

Summary and Conclusions. 1. The effect of psychotherapy without the use of calculated diets has been studied in 38 obese patients, and the results compared with obese patients treated by means of calculated diets, amphetamine and thyroid substance.

2. Psychotherapy resulted in a higher percentage of successful results than other methods studied.

3. All obese patients studied were found to have some type of psychoneurosis in varying degrees.

4. Psychotherapy and re-establishment of proper dietary habits is essential for permanent weight reduction.

REFERENCES

1. BRONSTEIN, I. P., WEXLER, S., BROWN, A. W., and HALPERN, L. J.: *Am. J. Dis. Child.*, **63**, 238, 1942.
2. BRUCH, H.: *Am. J. Dis. Child.*, **59**, 739, 1940.
3. CUTTING, W. C.: *J. Clin. Endocrinol.*, **3**, 85, 1943.
4. DANOWSKI, T. S., and WINKLER, A. W.: *AM. J. MED. SCI.*, **208**, 622, 1944.
5. GRAY, H.: *Stanford Med. Bull.*, **1**, 195, 1943.
6. GREENE, J. A.: *Ann. Int. Med.*, **12**, 1797, 1939.
7. HEINBECKER, P., WHITE, H. L., and ROLF, D.: *Am. J. Physiol.*, **141**, 549, 1944.
8. NEWBURGH, L. H.: *Arch. Int. Med.*, **70**, 1033, 1942.
9. PELNER, L.: *Ann. Int. Med.*, **22**, 201, 1945.
10. SCHOPBACH, R. R., and MATTHEWS, R. A.: *Arch. Neurol. and Psychiat.*, **54**, 157, 1945.

THE VALUE OF SPERANSKY'S METHOD OF SPINAL PUMPING IN THE TREATMENT OF RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS*

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RHEUMATIC fever and its sequelæ constitute a serious problem, particularly in the Scandinavian countries, Great Britain and the United States. This disease attacks chiefly children and young adults, who should be important economic assets. In Sweden, where the disease is notifiable, it is apparent that every year there are from 1500 to 2000 new cases per 1,000,000 of the population, while in the United States, Cecil⁴ states that 170,000 cases (more than 800 per 1,000,000) are reported annually.

The etiology of rheumatic fever is still unknown. Streptococci, septic foci, bowel intoxication, malnutrition, climatological factors and allergy, each in turn, have been held responsible for exciting this disease. Apart from the relief afforded by salicylates, the treatment of the heart and joint lesions is still unsatisfactory, and it is not possible at present to prevent the chronic invalidism resulting from the involvement of the heart or of the joints.

That chronic inflammation with its attendant fibrosis can be resolved without operative interference is not generally accepted. On this basis, therefore, subacute and chronic rheumatism doom individuals to life-long handicap. However, there is some evidence to show that excess fibrous tissue in arteries and even in organs may resolve spontaneously under favorable conditions. We have seen a sclerotic partially calcified uterine blood vessel

soften during pregnancy. Similar reactions have also been noticed in the ovary. Despite the highly specialized nature of these vessels, we are satisfied that the sclerosis yields sufficiently to a proper stimulus to allow the vessels to cope with the great functional needs imposed by a pregnant uterus. Similarly Cameron and Karunaratne³ have indicated in their experiments that the fibrosis induced in the liver by chronic carbon tetrachloride poisoning, at a certain stage, is reversible. More recently, Bogomolets² by means of his, anti-cytotoxic sera claim to resolve those fibrotic reactions characteristic of aging. These isolated observations reveal that by a correct approach it may not be impossible to facilitate the absorption of the fibrous tissue characteristic of the lesions of chronic rheumatism and arteriosclerosis.

The present traditional approach to disease, which has thrown much light on many pathological processes, has thus far proved inadequate in solving a variety of puzzling and crippling diseases, like rheumatism. Speransky,^{5,8} one of Pavlov's students, has emphasized the rôle of the nervous system in the causation of disease and in determining many manifestations not otherwise satisfactorily explained. By accepting as a working hypothesis that disease is not merely an expression of deranged normal function but indeed is an entirely new phenomenon having no counterpart in health, he was led to adopt

* This study of a unique therapeutic approach to "Rheumatism" reached our office after being 8 months in transit. The distance from Johannesburg precludes further correspondence before publication. The assessment of an unusual new therapy in arthritic conditions, particularly when it is without apparent fundamental rationale, is difficult. Of this the authors are well aware, for they have approached their subject objectively. They recognize the possibility that such factors as other medicaments used, autosuggestion, widely varying concepts of "rheumatism" in different countries and so on, might easily cloud their judgments of the effects of their specific therapy. Nevertheless, they have placed their observations on record in the hope that others may add further data to the problem before final opinion is rendered —THE EDITORS.

unorthodox procedures in studying pathological processes and in fashioning entirely new therapeutic methods. One method introduced by Speransky into clinical medicine is "spinal pumping." This he has applied in the treatment of 100 patients with polyarthritic rheumatism. Of these, 52 were treated during their first acute attack of rheumatic fever; 36 (70%) recovered completely; 33 had suffered more than one attack and of these 23 (73%) had no further attacks, and of 15 cases with chronic arthritis recovery was noted in 4 cases, improvement in 9, while 2 remained unchanged.

Comparing these results with those following the treatment of 127 cases of rheumatic fever with salicylates alone, Speransky remarks that, of the latter group, only 61 (48%) recovered completely.

Speransky moreover draws attention to the fact that "the first signs of objective and subjective improvement were noted within 10 hours after pumping in 27% of all cases and within 48 hours in more than 80%. Within 48 hours, objective changes had completely disappeared in 24 cases and in 18 of these there were no subjective complaints."

We have for some time devoted our attention to the problem of the rôle of the nervous system in disease, and in view of the dramatic changes observed by Speransky in cases of rheumatic fever treated by spinal pumping, we decided to examine the efficacy of his methods in the treatment of this common and devastating disease.

Spinal pumping seemed to many of the clinicians in Johannesburg such an unorthodox form of treatment, that we experienced considerable difficulty in obtaining cases of acute rheumatism with early involvement of the heart despite the fact that our experience indicated that at this early stage, rheumatism might respond most satisfactorily. We were therefore allowed to perform spinal pumping only on those cases which were resistant to all other forms of treatment. The results obtained were so remarkable that we feel

obliged to report our findings, especially as at present there is little likelihood of our being able to test out this method on a large series of cases under controlled conditions. We realize that 70 cases of the type available to us are obviously insufficient to allow of a proper assessment of the value of spinal pumping, but in view of some of the dramatic effects obtained and in view of the limited numbers of cases available in Johannesburg, we think that the publication of this report might perhaps encourage other workers in more favorable circumstances to test out on a large scale a therapeutic measure which, in our opinion, has the possibility of bringing relief to many individuals suffering from rheumatism.

Material. This report is based on the study of 70 patients suffering from acute, subacute or chronic forms of rheumatism with joint involvement. All the patients, with 3 exceptions, were adults.

Twelve of the 70 patients were treated during their first attack of acute rheumatic fever. In all patients, several of the large joints were swollen and exquisitely painful.

The 36 patients with subacute arthritis all complained of swelling, pain and limitation of movement in large and small joints, especially the knees, wrists, elbow, shoulder, metacarpophalangeal and interphalangeal articulations of varying duration. In 32 of the patients, the arthritis had started with an acute attack of rheumatic fever, associated with pyrexia, acutely swollen, painful large joints. The acute attack resolved slowly and then only partially. Residual lesions of varying severity were localized chiefly in several large joints as well as the small joints of the hands. Patients were rarely free from swelling and pain and the movements of the affected joints were limited. The majority of these subjects had already been treated in the usual way with typhoid or protein shock, diathermy, gold, aluminum or bee venom injections, diet and even hyperthermia and other forms of physiotherapy. It was only after these methods had brought no relief that spinal pumping was attempted. The arthritis in the remaining 4 subjects in this group, could, in our opinion, be regarded as entirely different

from that commonly seen in rheumatism. In these 4 cases the disease started soon after a severe emotional shock. The onset was not acute nor was it associated with swelling, pain or pyrexia. On the contrary, there was a gradual limitation of movement followed later by pain, deformity and contracture. The response to spinal pumping too, indicated a different etiology.

The 22 chronic arthritics in the main were over the age of 40 years, with a history extending over 3 or more years. The deformities were severe and radiologic examination revealed gross bony changes in and around the affected joints. In addition to the grossly distorted joints, 12 of the patients gave a history of recent swelling of joints in which only mild bony changes were visible radiologically. In most instances there were other signs usually found in chronic rheumatism, namely, trophic changes in the skin and muscles around the affected joints, thenar and hypothenar erythema, and vascular spiders.

Methods. In all but 2 instances, 10 gm. of sodium salicylate in divided doses were administered orally or rectally 24 hours before pumping and for 24 to 48 hours afterwards. In view of the effects on the bleeding tendency produced by large doses of salicylates,⁷ the prothrombin index was performed according to the method described by Stein⁹ on all those subjects taking salicylate for more than 3 days prior to the pumping.

The spinal pumping was performed in accordance with the method described by Speransky. However, as the technique of this procedure is described so briefly in his book and as we believe we have been able to overcome many minor difficulties, we offer no excuse for describing this method in detail.

Procedure. After inducing local skin anesthesia with 2% procaine, a lumbar puncture is performed with the patient in the left or right lateral position. Where the stiff joints made this position inconvenient, the sitting position was adopted.

A thin lumbar puncture needle with a very short bevel is ideal for this purpose, especially as it is essential to perform the lumbar puncture in such a way that the needle point lies *just* within the subdural space. After inserting the needle and when the cerebrospinal fluid flows freely, a good

10 cc. syringe (preferably all glass) is firmly attached.

The actual "pumping" consists in withdrawing into the barrel of the syringe 10 cc. of cerebrospinal fluid and re-introducing it into the subdural space. This procedure must be carried out so slowly that it takes at least $\frac{3}{4}$ to 1 minute to withdraw the fluid, and the same time to push it back. On no account should the fluid be forcibly extracted or hurriedly forced back. The fluid should flow so easily that only gentle traction on the plunger with one finger should be sufficient to cause continuous flow. When the pumping is executed with the patient in the sitting position, the pressure of the cerebrospinal fluid alone should be sufficient to push out the plunger of an all-glass syringe and no actual suction should be applied. In our cases 10 cc. of cerebrospinal fluid (only 6 cc. in children) were withdrawn and re-introduced 20 times. At the completion of the spinal pumping, 10 cc. of fluid were removed and discarded. The procedure should occupy 40 to 50 minutes.

If the fluid does not flow easily, it sometimes helps to introduce the needle a little deeper or withdraw it slightly by gentle traction. If the fluid still fails to flow freely the patient is gently raised into a sitting position. Usually, these procedures produce the desired effect, but sometimes it may be necessary to withdraw the needle completely and then re-introduce it through another intervertebral space.

Occasionally, when the fluid is being withdrawn, the patient complains of a sudden sharp twinge of pain referred down one or the other leg or to the coccyx. This sensation is consistently described as being "just like an electric shock." It passes off as quickly as it appears. This twinge invariably occurs when fluid is being withdrawn too rapidly. The operator experiences a definite impulse as if something has floated up against the needle point and, moreover, the flow of fluid is momentarily interrupted. It is probable that this sensation is caused by the sucking up against the needle of one of the nerves of the *filum terminale*. When this occurs it is advisable to re-inject 1 or 2 cc. of fluid and to pause for 10 to 15 seconds before proceeding with the extraction of the fluid; the needle should then be withdrawn slightly before attempting the next cycle.

Since this delicate manipulation may take

an hour to complete the operator should be comfortably seated.

Discussion. It is generally recognized that the swollen tender joints in acute rheumatic fever can disappear spontaneously in a most unpredictable fashion. It would seem, therefore, that but little reliance could be placed on the results obtained by spinal pumping. However, it is also known that, in many cases, despite all known forms of therapy over several weeks, the disease does not improve. It is our opinion that spinal pumping will hasten the relief in acute forms of rheumatic fever, especially as in this study, only cases were available in which other forms of therapy brought no relief and where the sedimentation rate remained persistently raised.

The assessment of improvement in the non-chronic cases was based on the general clinical condition, the temperature, pulse rate, sedimentation rate (1 hour Wintrobe method corrected for anemia), the diminution of swelling and pain, an increased range of movement of the affected limbs, together with any subjective information volunteered by the patient. In subacute cases, in addition, special attention was given to the peripheral circulation as expressed by the color and temperature of the fingers and toes and the atrophic, smooth, shiny skin over previously affected joints. The general improvement of the clinical condition as reflected by a gain in weight is sometimes an additional indicator of a remission in this disease.

The assessment of improvement in chronic cases is always extremely difficult, especially as such patients frequently have remarkable faith in any "new" treatment. They are usually mentally active and extremely eager to recover from their very crippling disease. Consequently, objective signs were relied upon and improvement was regarded as having taken place only in those patients in whom a very appreciable increase in the movement of one or more joints was noted, as well as a gain in weight, an increased appetite and restful sleep.

Regarding the terminology used in the assessment of the responses to spinal pumping, those patients in whom there were no objective signs of active disease were regarded as recovered. Those in whom there was a marked recovery of joint function in one or more joints, together with an associated drop in the sedimentation rate and a distinct amelioration in other signs and symptoms of the disease, were regarded as improved. The term "unchanged" is applied in this study to those cases in which there was no objective evidence of recovery.

Results. *Effects on the Joints.* The results in 70 cases are summarized in Table 1. Six of the 48 cases of acute and subacute arthritis showed no objective evidence of improvement. The remainder, however, were distinctly improved, although the rate of recovery varied in different patients. In 10% of those improved, the effects were noticeable immediately after the pumping was completed, as expressed by an increased movement and diminution of pain in the affected joints. The majority of patients (70%) was relieved within 12 to 36 hours, and another 20% responded at the end of 72 hours. The remaining cases showed a steady improvement which was maximal at the end of 2 to 3 weeks.

Although spinal pumping was followed by recovery of joints in which there were obvious pathologic changes in the bone, nevertheless, in acute attacks associated with pain and swelling superimposed upon the chronic lesion, this treatment curtailed the acute attack and apparently arrested the progress of the disease. For this reason, no recoveries among chronic cases are found in Table 1, but 12 of the 22 cases were considerably relieved. In general, therefore, the results obtained in this series of cases confirms those recorded by Speransky.

Relapses. Unfortunately, in Johannesburg, there is no organized service for the proper treatment and extended surveillance of patients suffering from the various manifestations of rheumatic fever. As a

consequence, it was possible to follow out the end results of spinal pumping only in 29 cases, for periods varying from 2 weeks to 18 months.

Eleven acute and subacute cases were under observation for 2 to 6 weeks. Of the 4 acute arthritics, 1 has remained well for the last 18 months while 3 relapsed within 7 to 16 days. It must be stated, however, that the relapse was only partial and after a second pumping these 3 patients have maintained good health for the past 8 to 18 months.

3 months later the patient relapsed again and spinal pumping was then without effect. This is the only patient in this series where a repeated spinal pumping failed to produce an effect after the first and second pumping had proved successful.

Of the 18 cases of acute, subacute and chronic arthritis who responded to spinal pumping and who have been under observation for 4 to 18 months, the disease has progressed in only 1 instance, and this in a patient with chronic arthritis.

TABLE 1.—CONDITION FOLLOWING TREATMENT

Type of arthritis	No. of cases	Responses			
		Recovered	Improved	Relapses	Unchanged
Acute	12	10	..	3	2
Subacute	36	28	4	3	4
Chronic	22	..	12	2	10
Total	70	38	16	8	16

Four of the 8 subacute cases experienced a partial relapse within 6 weeks, but after the second pumping 3 have remained well up to the present (8 to 18 months), while the fourth was pumped a third time and has suffered no further setback over the last 16 months. In addition to these, 8 other patients suffering from subacute arthritis who left the hospital within a few days after the first pumping have been under observation for 6 to 18 months. Two relapsed partially and the 1 who submitted to a second pumping has remained well for the past 5 months. The other patient regarded the degree of discomfort as so slight in comparison with the initial lesions that he did not feel inclined to have a second treatment unless the residual lesion progressed, which it has not done during the 4 month period of observation.

In the chronic cases, 6 were followed over 4 to 18 months. Two of these improved for a short period of time and then deteriorated. One of these patients showed a remarkable improvement during the first 6 months. Thereafter, both ankles became swollen and a spinal pumping was again performed with good result. However,

On the basis of this small group in which follow-up studies were possible, it would appear that: first, a single spinal pumping can be followed by lasting beneficial effects; second, when a relapse occurs it is usually not as severe as the initial attack; and, third, if spinal pumping induces salutary effects on 1 occasion then a second or even a third pumping is indicated in the presence of refractory joints or if a partial relapse occurs. Moreover, there is suggestive evidence that spinal pumping may arrest the progress of subacute or chronic arthritis.

Effects on Other Systems. *Peripheral Vascular System.* One of the remarkable features of spinal pumping, not mentioned by Speransky, is the profound effect on the peripheral vascular mechanism. This is expressed by severe sweating, a rise in skin temperature and a marked dilatation of the capillaries with noticeable pulsation, especially in the fundus oculi. Many of these reactions may occur after the tenth or twelfth cycle of pumping, but in the majority of patients they appear within a few hours after the treatment.

The extent of the perspiration varies

considerably. In some the skin over the whole of the body becomes clammy, whereas in others the patient may actually soak the bedclothes. This reaction may continue for as long as 48 hours.

During, or soon after the pumping, the extremities too, become appreciably warm or even hot. During the early stages of this study it was not possible to obtain accurate records of this phenomenon; however, in a few cases, the records of the skin temperature demonstrated that the temperature could be elevated by as much as 20° F. above the initial level, and that this full dilatation of the peripheral vessels could be sustained for 6 hours. The degree and duration of the dilatation of the peripheral vessels is much greater than is usually achieved after sympathetic blocks. Even the patients were conscious of this increase in warmth and they themselves frequently remarked that they had not experienced such warm extremities for years.

This effect was maintained for many months in patients who responded favorably, and even those whose joints had shown no improvement were glad of the relief from discomfiture of cold hands and feet. Apart from these visible effects on the peripheral blood vessels inspection of the retina has revealed marked pulsation of both arteries and veins immediately after pumping. In 1 patient suffering from weekly attacks of severe migraine, the spinal pumping precipitated a violent attack which persisted for 2 days. Since then, however, the patient has not complained of migraine for the past 12 months.

Since spinal pumping has widespread influence on the vascular mechanism there seems little doubt that these reactions are manifestations of a profound disturbance in the central nervous system, simulating the clinical picture of concussion. This similarity is further emphasized by the frequent interference with the heat regulating mechanism. In 20 cases of subacute arthritis with normal temperatures, spinal pumping resulted within 8 to 18 hours in an elevation of the temperature from

1° to 5°, lasting for 4 to 12 hours. In 2 patients there was a remittent pyrexia for 2 days, but this settled without any specific treatment. These alterations in the body temperature after pumping are in no way related to the nature and extent of improvement in the affected joints and the pyrexia itself cannot be considered as the important factor in the relief in the joints, as is said to be the case in shock therapy. This is supported by the fact that less than a third of the patients experienced pyrexia, and, moreover, the same patient may, on 1 occasion, show a marked rise in temperature and after a second pumping there may be no reaction of this nature. Similarly, in other subjects at the first pumping, there was no rise in temperature, but, on a subsequent occasion, it was raised. It is not possible to predict when a rise in temperature will occur or to correlate such instabilities of the temperature with any subjective or objective improvement.

Spinal pumping has a totally different effect where the temperature is elevated in acute attacks of rheumatic fever, especially where the temperature has remained elevated for several weeks, despite liberal doses of salicylate. In 10 such instances, after the spinal pumping, the temperature dropped by crisis.

There were a number of incidental beneficial effects following pumping which might be related to the disturbance in the peripheral vascular mechanism. Of special interest is the disappearance in 7 cases of long-standing skin rashes. In 6 of these the rash was of the sudaminal variety and, despite the profuse sweating which persisted for several days after the pumping, these rashes, generally thought to be caused directly by the sweating, cleared within 24 hours. In 1 instance, multiform acneform pustules on the face, abdomen and especially the back, were absorbed within 12 hours and could be recognized only as dull reddish-brown pigmented plaques.

The improvement in the joint lesions was always reflected by a diminution in

consequence, it was possible to follow out the end results of spinal pumping only in 29 cases, for periods varying from 2 weeks to 18 months.

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Chronic	22	..	12	2	10
Total	70	38	16	8	16

Four of the 8 subacute cases experienced a partial relapse within 6 weeks, but after the second pumping 3 have remained well up to the present (8 to 18 months), while the fourth was pumped a third time and has suffered no further setback over the last 16 months. In addition to these, 8 other patients suffering from subacute arthritis who left the hospital within a few days after the first pumping have been under observation for 6 to 18 months. Two relapsed partially and the 1 who submitted to a second pumping has remained well for the past 5 months. The other patient regarded the degree of discomfort as so slight in comparison with the initial lesions that he did not feel inclined to have a second treatment unless the residual lesion progressed, which it has not done during the 4 month period of observation.

In the chronic cases, 6 were followed over 4 to 18 months. Two of these improved for a short period of time and then deteriorated. One of these patients showed a remarkable improvement during the first 6 months. Thereafter, both ankles became swollen and a spinal pumping was again performed with good result. However,

On the basis of this small group in which follow-up studies were possible, it would appear that: first, a single spinal pumping can be followed by lasting beneficial effects; second, when a relapse occurs it is usually not as severe as the initial attack; and, third, if spinal pumping induces salutary effects on 1 occasion then a second or even a third pumping is indicated in the presence of refractory joints or if a partial relapse occurs. Moreover, there is suggestive evidence that spinal pumping may arrest the progress of subacute or chronic arthritis.

Effects on Other Systems. *Peripheral Vascular System.* One of the remarkable features of spinal pumping, not mentioned by Speransky, is the profound effect on the peripheral vascular mechanism. This is expressed by severe sweating, a rise in skin temperature and a marked dilatation of the capillaries with noticeable pulsation, especially in the fundus oculi. Many of these reactions may occur after the tenth or twelfth cycle of pumping, but in the majority of patients they appear within a few hours after the treatment.

The extent of the perspiration varies

considerably. In some the skin over the whole of the body becomes clammy, whereas in others the patient may actually soak the bedclothes. This reaction may continue for as long as 48 hours.

During, or soon after the pumping, the extremities too, become appreciably warm or even hot. During the early stages of this study it was not possible to obtain accurate records of this phenomenon; however, in a few cases, the records of the skin temperature demonstrated that the temperature could be elevated by as much as 20° F. above the initial level, and that this full dilatation of the peripheral vessels could be sustained for 6 hours. The degree and duration of the dilatation of the peripheral vessels is much greater than is usually achieved after sympathetic blocks. Even the patients were conscious of this increase in warmth and they themselves frequently remarked that they had not experienced such warm extremities for years.

This effect was maintained for many months in patients who responded favorably, and even those whose joints had shown no improvement were glad of the relief from discomfort of cold hands and feet. Apart from these visible effects on the peripheral blood vessels inspection of the retina has revealed marked pulsation of both arteries and veins immediately after pumping. In 1 patient suffering from weekly attacks of severe migraine, the spinal pumping precipitated a violent attack which persisted for 2 days. Since then, however, the patient has not complained of migraine for the past 12 months.

Since spinal pumping has widespread influence on the vascular mechanism there seems little doubt that these reactions are manifestations of a profound disturbance in the central nervous system, simulating the clinical picture of concussion. This similarity is further emphasized by the frequent interference with the heat regulating mechanism. In 20 cases of subacute arthritis with normal temperatures, spinal pumping resulted within 8 to 18 hours in an elevation of the temperature from

1° to 5°, lasting for 4 to 12 hours. In 2 patients there was a remittent pyrexia for 2 days, but this settled without any specific treatment. These alterations in the body temperature after pumping are in no way related to the nature and extent of improvement in the affected joints and the pyrexia itself cannot be considered as the important factor in the relief in the joints, as is said to be the case in shock therapy. This is supported by the fact that less than a third of the patients experienced pyrexia, and, moreover, the same patient may, on 1 occasion, show a marked rise in temperature and after a second pumping there may be no reaction of this nature. Similarly, in other subjects at the first pumping, there was no rise in temperature, but, on a subsequent occasion, it was raised. It is not possible to predict when a rise in temperature will occur or to correlate such instabilities of the temperature with any subjective or objective improvement.

Spinal pumping has a totally different effect where the temperature is elevated in acute attacks of rheumatic fever, especially where the temperature has remained elevated for several weeks, despite liberal doses of salicylate. In 10 such instances, after the spinal pumping, the temperature dropped by crisis.

There were a number of incidental beneficial effects following pumping which might be related to the disturbance in the peripheral vascular mechanism. Of special interest is the disappearance in 7 cases of long-standing skin rashes. In 6 of these the rash was of the sudaminal variety and, despite the profuse sweating which persisted for several days after the pumping, these rashes, generally thought to be caused directly by the sweating, cleared within 24 hours. In 1 instance, multiform acneiform pustules on the face, abdomen and especially the back, were absorbed within 12 hours and could be recognized only as dull reddish-brown pigmented plaques.

The improvement in the joint lesions was always reflected by a diminution in

the sedimentation rate. Frequently the sedimentation rate increased during the first week, and, thereafter, settled rapidly to normal. Usually, in those with persistently raised sedimentation rates who responded to pumping, the sedimentation rate returned to normal within 2 weeks, although it had previously remained elevated, despite the administration of massive doses of salicylates.

This favorable effect on the sedimentation rate was associated with a noticeable improvement in the general condition of the patient. The weight increased, the appetite was regained and sleep became restful. The protocols of 2 cases, 1 with subacute arthritis and 1 with acute rheumatic fever, are included here to indicate the nature of the responses observed.

Case Abstracts. *CASE 1. Subacute Rheumatoid Arthritis.* Male, aged 33, with extensive bilateral affection of knees, ankles, shoulders, wrists and hands. All these joints were swollen, extremely painful and movement was so limited that the patient had to be fed. The patient had been in the ward for 4 months and had been treated with salicylates, protein shock, gold, arthritin, aluminum acetate, bee venom and physiotherapy, without any result. On the day of pumping (May 6, 1943), he could not flex his fingers, wrists, elbows or knees, the right arm could not be abducted at all and the left could only be abducted 15 to 20°. The patient stated that he had such severe pains in all his joints that he could not sleep. Sedimentation rate (corrected for anemia, 1 hour Wintrobe) 52 mm. A total of 120 gr. of sodium salicylate were administered in 4 hourly doses for 24 hours before, and for 24 hours after, pumping.

Pumped 15 times at 6 P.M., May 6, 1943. On the morning of May 7th the patient was very bright; he slept well and could now flex hands, fingers and knees. The pain had been considerably alleviated and the swelling of these joints had subsided. On May 8th he walked for the first time since entering hospital; but, on walking, complained of pain in the right ankle. Patient continued to be well for the following 3 weeks and then the right elbow again became swollen. Salicylates were again administered for 24 hours and

the patient was pumped on May 28th. Full movement recovered 12 hours later. Joints remained well and patient's general condition improved remarkably. On June 4th sedimentation rate (corrected) was 22 mm. Patient was detained until June 23rd in excellent condition. There was some residual tenderness of the third and fourth metacarpophalangeal joints of the right hand. Sedimentation rate on June 23rd was 10 mm. On August 14th patient was seen again and was still well.

CASE 2. Acute Rheumatic Fever. A 23 year old female was admitted with acute rheumatic fever and arthritis affecting chiefly the right hand, the thumb and wrist, left shoulder, right knee and ankle. She was treated with local applications and 2 gm. of sodium salicylate 4 hourly for 2 weeks with slight improvement. However, on July 27, 1943 the left ankle and left knee became swollen and the temperature was still elevated to 101°. Sedimentation rate (corrected) was 42 mm. on July 26th. Spinal pumping was performed on July 29th at 4.30 P.M. During the night she developed a severe frontal headache. At 11 A.M. on July 30th the bandages were removed and patient, to her surprise, could flex her joints completely. The swelling of the left ankle and knee had disappeared and that of the right knee and ankle had subsided considerably. The left shoulder was still slightly tender to pressure but the movement had improved considerably. The temperature was now normal and remained so until the patient was discharged. On August 2d the patient got up and walked around without any pains at all. Grip of right hand now normal. Sedimentation rate on August 9th was 16 mm. Patient reported back on October 20, 1943 and June 16, 1944 and stated that she had been well and indulged in all forms of exercise. There were no objective signs of arthritis in any of the affected joints on June 16, 1944.

Miscellaneous Effects. Several untoward reactions following spinal pumping noticed by us were not mentioned by Speransky. Severe headache in 20 instances and vomiting in 10 were the commonest complications. At first, such headaches were regarded as due to low pressure following the removal of the 10 cc. of fluid.

Actually, the pressure very often rose steadily during the pumping and, at the end of the 20th injection of the fluid, it was frequently 100 to 150 mm. higher than at the outset. With the extraction of 10 cc. at the end of the pumping the pressure returned to normal. It is likely, however, that, after the initial generalized vasomotor disturbance, the pressure may fall and so evoke the low-pressure headache, which as a rule appears within 4 to 6 hours after pumping. There is, of course, the possibility that the pumping may stimulate an increased secretion of cerebrospinal fluid and the resulting headache would then be due to increased intracranial pressure. Although no observations were made on the cerebrospinal fluid pressure during these headaches, from the responses to fluids, drugs and posture it would appear that the headaches may be due in some patients to low, and in others, to increased pressure. That some form of cerebral irritation is induced is evident from the vomiting as well as photophobia and even pyrexia which may sometimes be associated with severe headache. It must be remembered, however, that salicylates *per se* may cause severe vomiting through its effects on the stomach or liver or even *via* the central nervous system. Relief from the headache may be satisfactorily provided by judicious administration of barbiturates and codein or, in some instances, of caffein intravenously.

The fact that the vascular mechanism in the brain is apparently disturbed profoundly by spinal pumping is a matter of some importance, especially as it may determine the type of case suitable for pumping. Speransky draws attention to some of his experimental findings that, if in dogs *all* the cerebrospinal fluid is repeatedly withdrawn and re-introduced, then the fluid may become blood-stained and acute hemorrhages occur in the brain itself. Red blood cells were not identified microscopically in the cerebrospinal fluid removed from 20 cases after pumping. In the remaining cases the fluid was macroscopically normal. However, in view of

the profound cerebral vasodilation which appears to be a notable reaction to pumping it is likely that, in the presence of hypertension or cerebral vascular disease, the increased strain on the arterioles may result in a cerebral hemorrhage. This possibility is suggested by the occurrence of multiple cerebral hemorrhages in a patient after spinal pumping. A summary of the clinical history and autopsy findings in this patient is as follows:

Clinical Summary. The patient, a female aged 45, was admitted to hospital with a typical attack of rheumatic fever which developed 3 weeks after a Pott's fracture of the left leg. All the large joints were swollen and exquisitely painful. The blood pressure was 168/110. The temperature remained elevated for 17 days, despite the continued administration of 120 to 180 gr. of sodium salicylate throughout this period. The joints were extremely painful throughout, and the pain could only be alleviated by repeated administration of morphine. In view of the hypertension and our knowledge that pumping results in dilatation of cerebral vessels it was thought unwise to perform a spinal pumping. However, in view of the fact that the patient was not responding to treatment, as well as the absence of any record by Speransky of any untoward events following this procedure in man, we finally decided to perform spinal pumping. This was done even more slowly than usual.

The temperature came down by crisis within 16 hours of pumping and the patient was extremely pleased with the relief from the severe joint pains which accompanied the diminution in the swelling and the increased movement. The patient complained of a severe headache for the next 14 hours, which was considerably relieved by 2 tablets of A.P. Cod., 4 hourly: The temperature during this period remained normal and continued thus for the next 3 weeks. Whereas the knees, right ankle, wrists, shoulders and right elbow returned to normal within 48 hours of the pumping, the left elbow, although it had improved considerably, remained slightly swollen and painful. During the next 2 weeks the joints became progressively worse and the pain returned to the left shoulder. In view of the excellent response obtained with the first pumping

and the absence of any unusual reactions, it was decided to repeat the treatment. Salicylate therapy, which was discontinued 48 hours after the first pumping was again instituted and 48 hours later a second pumping was performed. This time 10 cc. of fluid were extracted and reinjected only 10 times. Within 16 hours the patient had recovered full movement in the left elbow and shoulder and the joints appeared objectively normal. The patient again complained of headache but was otherwise bright and very pleased with the result. Twenty hours after the pumping the temperature rose to 101° but the patient, although flushed, still felt perfectly happy. This temperature was remittent for the next 48 hours and on the 3d day after pumping the patient became drowsy and giddy and during the next 12 hours became stuporous and then comatose. Lumbar puncture at this time revealed a negative pressure of 15 mm. The breathing was now stertorous, the pulse was rapid and bounding and the temperature had risen to 104° . There were no localizing signs, the pupils remained equal and dilated until death. Blood pressure at this time was 180/110. The patient never recovered from coma. Respiration failed at 10 P.M. of the 3d day after the second pumping and artificial respiration was instituted, together with repeated injections of picrotoxin and adrenalin. The circulation was maintained actively until 2 A.M. the following morning when it slowly failed.

Autopsy: This revealed multiple small cerebral hemorrhages in the occipital and frontal lobes, together with numerous fine petechial hemorrhages scattered throughout the brain substance. The basal cerebral vessels showed no signs of degenerative disease. However, the myocardium was thickened, due to hypertrophic changes. Death was due to cerebral hemorrhage.

The strange mode of onset of the hemorrhages and the unusual sites, as well as the fact that these became clinically recognizable for the first time only 3 days after the second spinal pumping, made it extremely difficult to assess the part played by the pumping and the hypertension in the production of the cerebral catastrophe. It was considered that the hypertension, together with the increased

cerebral vascularity which we think was to be produced by the pumping, might have resulted in the bursting of the weakened vessels in the frontal and occipital regions.

However, Ashworth and McKemie recently reported¹ 2 patients who died from multiple cerebral hemorrhage following salicylate therapy alone. The probability presents itself, therefore, that death in our single case was in no way attributable to pumping but was rather the result of the capillary damage and hypoprothrombinemia produced by salicylate poisoning.

Since this accident, we now regard any signs of vascular disease as a contraindication for spinal pumping; but it still remains to be firmly established whether this is justified or not.

Indications for Spinal Pumping. On the basis of our experiences as well as of those from the limited records available to us in Speransky's book,⁸ we recommend spinal pumping under the following conditions, in order of importance:

1. In patients suffering from a first attack of acute rheumatic fever who have not responded to treatment with 90 to 180 gr. of sodium salicylate daily for 2 to 3 weeks.

2. In subacute arthritis following an attack of acute rheumatic fever where the disease has been present for less than 18 months. Early bony changes, while not a contraindication to this form of therapy, militate against the excellent responses observed in subjects without any involvement of the bones.

3. In chronic arthritis where new joints previously unaffected have recently become involved.

4. In chronic arthritis in which the cold extremities are a source of great discomfort.

Contraindications to Spinal Pumping.

1. Until disproved, the presence of any form of vascular disease in which the cerebral vessels may be implicated must be regarded as a contraindication to pumping.

2. Complete destruction of joints.

3. A low prothrombin index, due either

to prolonged salicylate therapy, or to the hepatic disease that is so frequently present in chronic arthritis.

In 3 cases of acute gonococcal arthritis spinal pumping was ineffective. Moreover, spinal pumping is also ineffective in those forms of arthritis in which swelling of the joints is apparently secondary to intra-articular disease. In our opinion, this arthritis is unrelated to rheumatic fever and usually commences as a gradual contraction of the joints following a severe emotional storm.

Comment. The nervous system is not generally considered to play more than a subsidiary part in inflammatory processes. Even where the nervous component of an inflammatory process is admitted it is regarded as an auxiliary factor capable only of exerting an indirect influence on the course of the inflammation and not on its quality. By a series of brilliant experiments, Speransky arrived at the opinion that, not only does the nervous system play more than a minor part in inflammation, but the course, if not the genesis, of the inflammation is directly determined by the nervous system.

When rheumatic fever expresses itself in the form of chorea it is generally believed that the nervous system in such instances is involved in the same way as any other part of the body. The peculiar reactions seen in chorea are regarded as a manifestation of a functional derangement resulting from a nervous form of rheumatism. However, when other parts of the body are affected by this strange disease, it is not generally appreciated that the nervous system is still implicated. Despite the fact that rheumatism is invariably associated with a generalized derangement of bodily function, as expressed by the pyrexia, irritability, vasomotor disturbances and metabolic changes, when it appears to be localized in the heart or the joints, attention is directed to the affected parts and the therapy is designed accordingly. The rôle of the nervous system in these circumstances is, as a rule, completely overlooked, and no

attempt is made to attack the disease by concentrating on this aspect of the organism.

There is scattered evidence that the nervous system plays a considerable rôle in the pathogenesis of rheumatic fever and rheumatoid arthritis, even when it is not so grossly involved as in chorea.⁶ This is illustrated especially by the muscular reactions and trophic changes which accompany rheumatoid arthritis. The atrophy of the muscles in this disease is usually attributed to disuse of the affected joints. However, the rapidity and extent of the wasting is out of proportion to the duration of the disease. Such rapid muscular atrophy is characteristic of nerve lesions. The fibrillation so commonly observed in the muscles around the affected joints in arthritis also suggests the implication of the nervous system and the typical trophic changes in the skin in rheumatism are similar to those usually described after nerve lesions.

That injury to the nervous system may be attended by metabolic disturbances is well known. However, it is not generally appreciated that the introduction of toxins into the nervous system can excite reactions in remotely removed organs similar to those encountered after the administration of the same toxins intravenously.⁵ Speransky has produced a type of carditis by the intrathecal administration of small doses of diphtheria toxin in a passively immunized animal, indistinguishable from that following severe diphtheria intoxication.^{5,8} It seems very likely that the carditis and arthritis as well as the other manifestations of rheumatic fever may in large measure result from a widespread involvement of the nervous system.

While relief must be provided to the parts of the body obviously affected by an attack of rheumatic fever, if lasting and effective treatment is desired, attention must be directed also, in our opinion, to the nervous system. Irrespective of its mode of action, there can be little doubt that spinal pumping produces some interference with the nervous mechanism and

can, and does lead to spectacular responses in the various forms of rheumatism resistant to the usual forms of therapy.

Since salicylates have been used in conjunction with pumping it might be argued that spinal pumping has so affected the blood brain barrier as to allow the increased penetration of this drug into the cerebrospinal fluid. This was the view which Speransky originally propounded, but later it was rejected when more experimental evidence was forthcoming. We have not been able to find any significant increase in the salicylate content of the cerebrospinal fluid immediately after, or even 24 hours after, spinal pumping. Moreover, the bromide test of the blood brain barrier which was performed in 6 cases who were pumped, failed to demonstrate an increased bromide content of the cerebrospinal fluid after pumping. The final proof that salicylates are not alone responsible for improvement is indicated by the fact that in 2 cases the response was no less effective *without* salicylates. These findings add further support to Speransky's hypothesis that spinal pumping acts directly on the nervous system.

Although, in the present stage of our knowledge, it is not possible to provide a scientifically plausible explanation for the mode of action of spinal pumping, nevertheless, the fact that, after pumping, a joint immobilized for many months is capable, within a few hours, of assuming full function is remarkable and has extremely important implications. The present orientation towards the factors responsible for immobilization of the joints in acute and subacute rheumatoid arthritis require to be reviewed in the light of these findings. It is evident that if the joints were fixed by fibrous tissue after a long period of immobility, it should be scarcely possible to induce movement within a few hours. The present methods adopted by orthopedic surgeons in manipulating joint contractures resulting from rheumatism are obviously not directed by any rational understanding of the patho-

logic processes in and around these diseased joints.

Although the rapid recovery of movement within a few hours of pumping cannot be attributable to a loosening of fibrous bands, nevertheless, we have evidence that the fibrous tissue in rheumatism can be absorbed, not only from the peri-articular regions, but also from other parts of the body. We have actually seen subcutaneous nodules disappear within 24 to 48 hours after pumping.

If fibrous tissue can disappear, as it does, from some parts of the body, then there is every reason to suppose that, at certain stages of the disease, spinal pumping may lead to the absorption of fibrous nodules from the heart and even from the valves. Speransky has drawn attention to the disappearance of murmurs in rheumatic fever after pumping. Unfortunately, up to the present we were only allowed access to such patients as would not respond to other forms of therapy. From our experience we are sufficiently optimistic to suggest that the most dramatic effects can be anticipated in the acute and subacute forms of rheumatism.

At present, when the heart is involved, treatment is palliative as there are no known methods of resolving or even arresting the progress of rheumatic pancarditis. While we do not, at this stage, recommend the universal application of this simple procedure, we do feel that a thorough investigation of spinal pumping in all forms of acute and subacute rheumatism under controlled conditions may prove to be invaluable in our attack on the devastating effects of rheumatism.

Finally in view of the effects of spinal pumping on the peripheral vascular system already described, it seems that this method may also be used to advantage in those diseases where it is desirable to excite a marked and prolonged dilatation.

Spinal pumping has proved effective in a variety of seemingly unrelated diseases.⁸ The fact that many of these diseases respond to a single non-specific method of therapy lends support to Speransky's con-

tention that, however divergent the pathologic processes in these diseases may appear to be, there is one feature common to all, namely, that the nervous system is significantly implicated to a greater or lesser extent. Speransky is responsible for redirecting our attention to this important part of the body and for providing a re-orientation in our understanding and attack on many diseases which, hitherto, have proved refractory to our present methods of therapy based on the orthodox concepts of disease.

Summary. Using spinal pumping in the treatment of 70 cases of acute, subacute and chronic rheumatism with arthritis, it was shown that in 38 of 48 cases of acute and subacute arthritis all objective and subjective signs of the disease disappeared, and 12 of 22 chronic cases were improved. In many instances, full function was regained within 4 days. These observations tend to confirm those recorded by Sper-

ansky in 100 cases with various forms of rheumatic polyarthritis.

Spinal pumping has a profound effect on the peripheral blood vessels leading to a prolonged vasodilatation.

Conclusions. It is suggested that, with due regard for the difficulties of evaluation, it appears that spinal pumping may arrest the progress of rheumatic fever, especially in the acute and subacute stages, and may be of value in the early stages of rheumatic pancarditis.

Since this study tends to confirm Speransky's observations on the value of spinal pumping in the treatment of the various manifestations of rheumatic fever, and in view of the significant changes induced in the peripheral vascular system by this form of therapy, we strongly recommend that this method be given further trials on a larger series of cases under controlled conditions.

We wish to acknowledge our great indebtedness to Prof. Raymond A. Dart for his interest and encouragement. Our thanks are due to Dr. L. I. Braun and Dr. N. V. Storr as well as Drs. B. Cohen, J. J. de Waal, T. Schneider, A. Koenig, S. Heiman and H. L. Heimann for allowing us access to their clinical material.

REFERENCES

1. ASHWORTH, C. T., and McKEMIE, J. F.: *J. Am. Med. Assn.*, **126**, 806, 1944.
2. BOGOMOLETS, A. A.: *Am. Rev. Soviet Med.*, **1**, 101, 1943.
3. CAMERON, G. R., and KARUNARATNE, W. A. E.: *J. Path. and Bact.*, **42**, 1, 1936.
4. CECIL, R. L.: *A Textbook of Medicine*, Philadelphia and London, Saunders, 1943.
5. GILLMAN, J., and GILLMAN, T.: Speransky's Analysis of the Rôle of the Nervous System in Disease, *Am. Rev. Soviet Med.*, **2**, 79, 1944.
6. LUHTWICH, L.: *Functional Pathology*, New York, Grune & Stratton, 1941.
7. SHAPIRO, S., REDISH, M. H., and CAMPBELL, H. A.: *Proc. Soc. Exp. Biol. and Med.*, **53**, 251, 1943.
8. SPERANSKY, A. D.: *A Basis for the Theory of Medicine*, Intra Coop. Pub. Soc. Moscow, 1935.
9. STEIN, H. B.: *South Africa J. Med. Sci.*, **6**, 93, 1942.

THE CHANGE IN PLASMA VOLUME AND BODY WEIGHT IN NORMAL SUBJECTS AFTER A LOW SALT DIET, AMMONIUM CHLORIDE AND MERCUPURIN*

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RECENT work^{11,12,13} has indicated that the plasma volume in normal subjects may fluctuate considerably with small changes in the fluid content of the body associated with the administration of sodium salts or the use of diuretics. Similar and more extensive changes in animals have also demonstrated the fact that the plasma volume is to a considerable extent dependent on the extracellular fluid volume.^{14,16}

Decreases in the fluid content of the body, produced by means of diuretics such as ammonium chloride or mercupurin, is the accepted treatment of edematous subjects. Though there has been considerable investigation of the biochemical action of ammonium chloride,^{3,5,6,9,10,17} there is little information available concerning the diuretic effect that might be expected in the non-edematous hospital patient on an unrestricted diet. In general, the same difficulty is encountered concerning the action of mercurial diuretics on normal subjects, though Blumgart *et al.*² did a careful study on a few subjects. The combination of acid salts with mercurial diuretics to enhance the diuretic action of both drugs has been extensively studied,^{4,8,9,15} but again little information is available concerning the effect of the combination of these drugs on the normal subject.

Such diuretics may serve as a means of

producing an experimental type of dehydration in normal subjects. They have been used in this study to demonstrate the changes in plasma volume associated with the loss of body fluid.

This report deals with the changes in body weight, plasma volume, serum protein concentration, and total circulating protein of normal subjects following the combined use of a low salt diet, ammonium chloride, and mercupurin. The diuretic action of the low salt diet and ammonium chloride alone and of mercupurin alone is compared to the effect of the combination of both drugs in the normal subject.

Methods and Materials. The effect of mercupurin alone on the plasma volume and body weight of 10 normal subjects was previously studied by determining these measurements before and 24 hours after intravenous injection of 2 cc. of the drug. The results have been described in detail elsewhere,¹³ and the change in body weight and plasma volume are included here for the purpose of comparison. The rôle of a low salt diet and ammonium chloride on plasma volume and body weight in 15 normal subjects also has been described.¹⁴ The 9 normal subjects reported here were selected from the above group largely because of their availability and willingness to continue the study. After control determinations, they were placed at bed rest and consumed a low salt diet (about 2.5 gm.) adjusted in calories to 40% above the estimated basal

* Supported by grants from the Board of Governors of the Horace H. Rackham School for Graduate Studies, and the Upjohn Company.

TABLE 1.—CHANGES IN PLASMA VOLUME, HEMATOCRIT, SERUM PROTEIN CONCENTRATION, TOTAL CIRCULATING PROTEIN AND BODY WEIGHT

	1	2	3	4	5	6	7	8	9
CONTROL DETERMINATIONS									
Plasma vol. (cc.)	2800	3090	2600	3030	3030	2560	3180	2730	3210
Hematocrit	35.7	46.2	42.0	41.2	45.9	39.1	44.5	44.9	49.3
Total protein concentration (gm. per 100 cc.)	7.13	6.82	6.16	7.79	5.85	7.06	7.20	7.06	
Total circulating protein (gm.)	199	211	160	236	177	181	229	193	70.1
Body weight (kg.)	42.0	80.0	44.0	58.5	43.3	53.3	52.0	61.2	
CHANGE FROM CONTROL DETERMINATIONS AFTER A LOW SALT DIET AND AMMONIUM CHLORIDE									
Change in plasma vol. with NH_4Cl from control determination	Mean: -403	St. dev.: 321	St. error: 114						
% change in hematocrit	Mean: -2.45	St. dev.: 9.26	St. error: 3.27						
% change in serum protein concentration	Mean: +3	St. dev.: 9.8	St. error: 3.69						
Change in body weight (kg.)	Mean: -1.76	St. dev.: 1.02	St. error: 0.36						
CHANGE WITH 2 CC. MERCUPURIN FROM VALUES FOUND AT THE END OF THE AMMONIUM CHLORIDE RÉGIME									
Change in plasma vol. with 2 cc. mercupurin from values after NH_4Cl administration	Mean: -329.4	St. dev.: 169	St. error: 59.7						
% change in hematocrit	Mean: +14.85	St. dev.: 8.01	St. error: 2.83						
% change in serum protein concentration	Mean: +15.2	St. dev.: 7.42	St. error: 2.80						
Change in body weight (kg.)	Mean: -2.14	St. dev.: 0.83	St. error: 0.29						
CHANGE RESULTING FROM BOTH AMMONIUM CHLORIDE AND MERCUPURIN COMPARED TO THE CONTROL DETERMINATION									
Total change in plasma vol. with NH_4Cl and 2 cc. mercupurin from control determinations	Mean: -730	St. dev.: 270	St. error: 95.4						
% change in hematocrit	Mean: +9.33	St. dev.: 6.74	St. error: 2.42						
% change in serum protein concentration	Mean: +17.47	St. dev.: 15.14	St. error: 5.71						
Total change in body weight (kg.)	Mean: -3.08	St. dev.: 0.33	St. error: 0.12						

caloric consumption. Nine grams per day of ammonium chloride in enteric coated tablets were ingested. At the conclusion of this régime which varied from 3 to 19 days, the measurements were repeated, and a 2 cc. intravenous injection of mercupurin was then given. The observations were again made 24 hours later to evaluate the effect of the mercupurin injection.

The subject was weighed in the rested postabsorptive state on a beam balance accurate to 2 gm. After the weighing he was placed on a table and blood was withdrawn for the determination of the plasma volume,⁷ hematocrit,¹⁸ and total serum protein concentration.¹ The total circulating protein may be calculated from the product of the plasma volume and the serum protein concentration.

Results. The alterations in plasma volume and body weight as well as the percentage change in plasma volume, hematocrit, serum protein concentration, total circulating protein and body weight are recorded in Table 1. The second portion of this table deals with changes resulting from the injection of mercupurin on the partially dehydrated subject.

With the administration of 2 cc. of mercupurin alone to 10 normal subjects on the normal diet, a weight loss of 1.73 ± 0.3 kg. ($2.6 \pm 0.5\%$) was produced in 24 hours, and it was associated with a loss in plasma volume of 544 ± 88 cc. or $15.7 \pm 2.4\%$.¹³ A low salt diet and ammonium chloride in the subjects reported here produced a greater weight loss of $3.1 \pm 0.58\%$ than that experienced by the subjects who received mercupurin alone. The decrease in plasma volume, however, was not as great in spite of the weight loss and amounted to 403 ± 11.4 cc. or $13.8 \pm 3.8\%$. The administration of mercupurin to these already dehydrated subjects produced a further loss of weight of $3.94 \pm 0.52\%$ which was considerably larger than that experienced by the normal subjects receiving mercupurin alone. The change in plasma volume was smaller in these dehydrated subjects and amounted to only 329 ± 59.7 cc. The relative change of plasma volume, $13.1 \pm 2.5\%$, was not significantly different

from the change in plasma volume with mercupurin alone.

The effect of the combined administration of the low salt diet, ammonium chloride, and mercupurin produced a decrease in the body weight from the control determinations of 3.68 ± 0.12 kg. or $6.7 \pm 0.4\%$. This was accompanied by a mean decrease in plasma volume of 730 ± 95 cc. or $25.2 \pm 3.96\%$.

For the purpose of comparison the mean change in plasma volume and body weight induced by: (1) a 2 cc. injection of mercupurin without previous preparation with ammonium chloride; (2) ammonium chloride and a low salt diet; (3) by 2 cc. intravenous injection of mercupurin following ammonium chloride administration; and (4) the total effect of the low salt diet, ammonium chloride, and 2 cc. of mercupurin are shown in Figure 1. It will be noted that the mean change in plasma volume following the injection of mercupurin in the subjects on a low salt diet and ammonium chloride (Column 3) was significantly smaller than that found in subjects on their usual diet who received a similar injection of mercupurin (Column 1). These changes may be more directly compared when expressed as mean percentage change from previous determination as illustrated in Figure 2. The third column represents mean percentage change produced by mercupurin from the values of plasma volume and body weight noted after the administration of ammonium chloride. The fourth column is the mean percentage change from the control determinations.

The mean percentage change in the serum protein concentration and total circulating protein are of considerable interest and are shown graphically in Figure 3. The serum protein concentration may increase to some extent with the loss of plasma volume resulting from dehydration, but the change is proportionately less than the change in plasma volume. Thus there is a loss of total circulating protein. This decrease in total circulating protein was noted when the plasma volume

Change in Plasma Volume and Body Weight

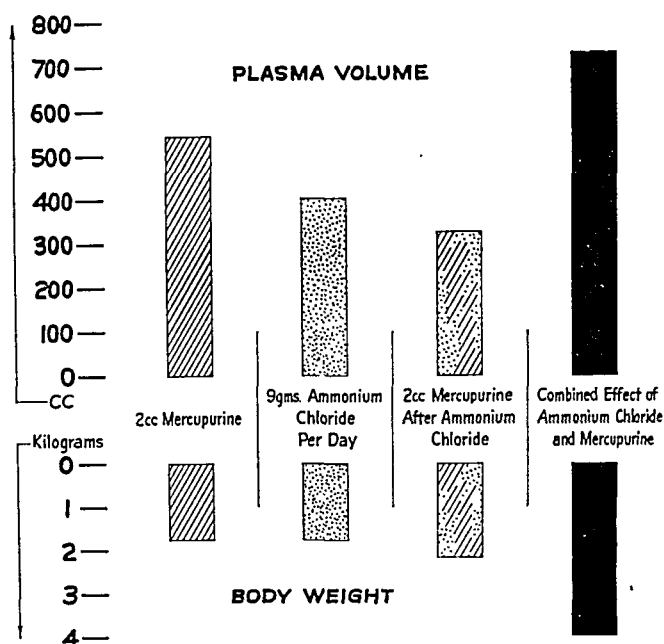


FIG. 1.—A comparison between the decrease in plasma volume and body weight in normal subjects after (1) 2 cc. of mercupurin; (2) a low salt diet and ammonium chloride; (3) after 2 cc. mercupurin from the values produced by the low salt diet and ammonium chloride; (4) the combined effect of the low salt diet, ammonium chloride followed by 2 cc. of mercupurin.

Percentage Change in Plasma Volume and Body Weight

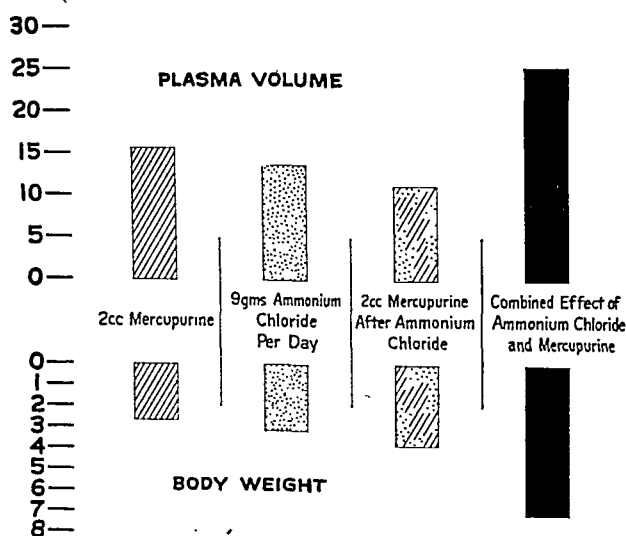


FIG. 2.—A comparison of the relative change in plasma volume and body weight in normal subjects after (1) 2 cc. of mercupurin; (2) a low salt diet and ammonium chloride; (3) 2 cc. mercupurin from the values produced by the low salt diet and ammonium chloride, and (4) the combined effect of the low salt diet, ammonium chloride, followed by 2 cc. mercupurin.

was decreased by mercupurin alone or by ammonium chloride. When mercupurin was administered after preparation with ammonium chloride, however, the total circulating protein did not change and the serum protein concentration increased considerably. It will also be noted in Figure 2 that under these circumstances in spite of a greater loss of water, there was less change in the plasma volume than might have been expected if as extensive a diuresis had resulted from mercupurin or ammonium chloride alone.

ing the ammonium chloride administration in spite of a good diuresis; both, however, experienced not only a good diuresis with mercupurin, but also greater loss in plasma volume than many of the other subjects.

Discussion. It is apparent from these results that the combination of a low salt diet and ammonium chloride followed by a 2 cc. intravenous injection of mercupurin will produce a considerable degree of dehydration in the normal individual which in these cases amounted to a mean loss

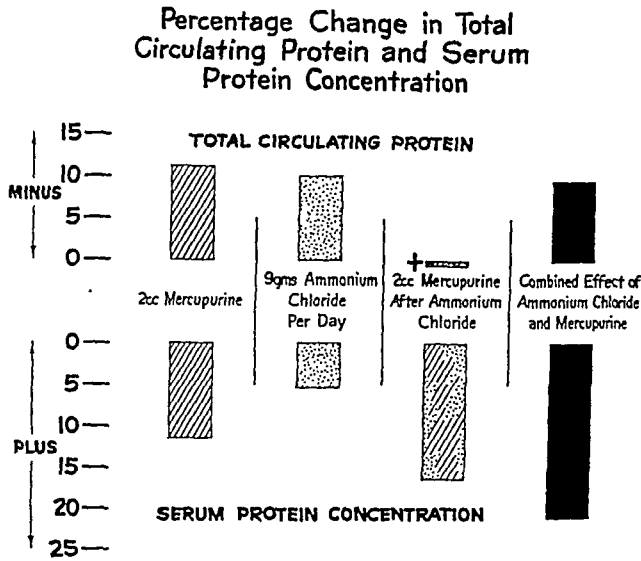


FIG. 3.—A comparison of the relative changes in total circulating protein and serum protein concentration after (1) 2 cc. mercupurin; (2) a low salt diet and ammonium chloride; (3) after 2 cc. of mercupurin from the values produced by the low salt diet and ammonium chloride, and (4) the combined effect of the low salt diet and ammonium chloride followed by 2 cc. of mercupurin.

With the administration of a low salt diet and ammonium chloride, the hematocrit in 8 of the cases completely failed to indicate the direction of change of the plasma volume or the extent of the change, and frequently fell as the plasma volume was decreased. Following the injection of mercupurin, however, the hematocrit closely reflected the further dehydration of the plasma volume, and in many instances the percentage change in plasma volume. Another point of some interest was the extent of the change in the plasma volume induced by mercupurin. Two cases (Nos. 3 and 7) did not have a significant change in the plasma volume follow-

ing the administration of a low salt diet and ammonium chloride, or 6.72±0.42% of the body weight. A diuresis of this degree is not uncommonly experienced in patients with heart failure and edema. Should such a diuresis occur in a formerly edematous patient, it should not necessarily be looked upon as evidence of "sub-clinical" edema.

It may also be noted that the diuretic effect of the low salt diet and ammonium chloride in the normal subjects was somewhat greater than that experienced with mercupurin alone. This is contrary to the usual clinical impression formed while dealing with edematous patients in whom mercupurin usually produces a greater

diuresis. This may be explained by the fact that with the administration of ammonium chloride to the normal subject there is a loss of both intracellular and extracellular fluid.^{3,5,10,17} The weight loss following mercurial diuretics is, on the other hand, almost entirely at the expense of the extracellular fluid.² It would seem likely then that in normal subjects ammonium chloride affecting both the extracellular and intracellular fluid compartments might produce a somewhat greater diuresis, while with edematous subjects where there is an excessive accumulation of extracellular fluid, a greater diuresis might be experienced with mercupurin.

In spite of a slightly greater weight loss, the change in plasma volume after ammonium chloride was somewhat less than that experienced after mercupurin alone. This might be expected if mercupurin has a greater effect on the extracellular fluid.

The weight loss in this group of 9 subjects with the low salt diet and ammonium chloride was not as great as that reported in a previous study of normal subjects who received the diet and ammonium chloride for a period of 3 to 4 days.¹¹ This may in part be due to the selection of cases since some of these cases had experienced relatively little diuresis early in the régime and therefore it was continued for a longer period before the plasma volume and body weight were again measured. It is apparent, however, that continuing the régime over several days does not significantly increase the loss of weight.¹¹

Of considerable interest was the diuresis experienced following mercupurin injection in these subjects who had already lost approximately 3% of the body weight on the low salt ammonium chloride regimen. The rôle of the acid salts in enhancing the diuretic effect of the mercurial diuretics is well known^{4,8,9,15} and it appeared to exert a similar rôle, as expected, in these normal subjects. The weight loss with mercupurin alone was $2.64 \pm 0.5\%$ of the body weight. On the other hand, the weight loss induced by mercupurin after preparation with a low salt diet and am-

monium chloride was $3.94 \pm 0.5\%$ of the body weight in spite of the associated dehydration with such a preparation. However, with the greater diuresis there was less change in the plasma volume than was noted after the administration of either ammonium chloride or mercupurin alone, Figure 2. With mercupurin alone, the loss of plasma volume accounted for $26.3 \pm 3.8\%$ of the loss of body weight; after ammonium chloride preparation the loss of plasma volume following injection of mercupurin accounted for only $16.5 \pm 4.2\%$ of the loss of body weight.

With the diuresis following the administration of ammonium chloride or the injection of mercupurin without previous preparation, the decrease in plasma volume was accompanied by a decrease in the total circulating protein and by a relatively small increase in the serum protein concentration as noted in Figure 3. On the other hand, the more extensive diuresis produced by mercupurin in the already dehydrated subject after ammonium chloride administration was not accompanied by a similar decrease in the total circulating protein and the fall in plasma volume of 13.1% was associated with an increase in the serum protein concentration of 15.2%. It would appear likely that this increase in the serum protein concentration prevented a greater decrease in the plasma volume under these circumstances even though there was a more extensive diuresis. The possibility is suggested by these findings that the total circulating protein may be quite labile with small losses of body fluid, but when greater degrees of dehydration occur the protein is held in the blood stream. There is probably a limit to the loss of plasma volume with dehydration due to the fact that the serum protein held in the blood stream in higher concentrations will support the plasma volume in spite of dehydration of the tissues.

The changes in the hematocrit appeared to be similar in many ways to the changes in the serum protein concentration. With the milder forms of dehydration the hem-

atocrit failed completely to indicate the changes in the plasma volume. This has been noted before.^{11,12,13,14} With further dehydration induced by mercupurin after the low salt diet and ammonium chloride there was a considerably greater change in the hematocrit which more closely reflected the further depletion in the plasma volume. It is possible that the measurement of plasma volume by the dye dilution method may reflect changes in the capillary circulation with mild dehydration before the relationship of cells to plasma in the large vessels is disturbed. When more extensive dehydration occurs, then the relationship of cells to plasma in large vessels will parallel the change in plasma volume.

All of these subjects exhibited some symptoms suggestive of an inadequate circulation on the day following the injection of mercupurin. They complained of weakness, prostration, fatigue, and some felt so faint in attempting to stand that they chose to remain in bed. There was a decrease in the pulse pressure and venous pressure and an increase in the basal pulse rate, though these were not regularly recorded in this group, which would also suggest a decrease in the volume of their circulation. In some instances, the dehy-

dration was so complete that it suggested the clinical and circulatory defect frequently noted in early shock.

Conclusion. The administration of a low salt diet, ammonium chloride, and mercupurin to 9 normal subjects resulted in a mean loss of 3.68 ± 0.12 kg. or $6.72 \pm 0.42\%$ of the body weight. This diuresis was associated with a mean fall in plasma volume of 730 ± 95 cc. or $25.17 \pm 3.9\%$. The diuretic effect in normal subjects of a 2 cc. injection of mercupurin, of a low salt diet and ammonium chloride and of a 2 cc. injection of mercupurin after preparation with a low salt diet and ammonium chloride are compared.

Though diuresis resulting from a 2 cc. injection of mercupurin is increased by the preparation with a low salt diet and ammonium chloride, the change in plasma volume under these circumstances is less pronounced. This may be associated with the fact that the preparation with a low salt diet and ammonium chloride produces an initial fall in plasma volume and total circulating protein. Subsequent loss of fluid is not followed by further decrease in total circulating protein so that the increased concentration of serum protein may tend to prevent larger changes in the plasma volume.

REFERENCES

1. BARBOUR, H. G., and HAMILTON, W. F.: *J. Biol. Chem.*, **30**, 289, 1917.
2. BLUMGART, H. L., *et al.*: *Arch. Int. Med.*, **54**, 40, 1934.
3. DENNIG, H., DILL, D. B., and TALBOTT, I. H.: *Arch. Exp. Path. and Pharm.*, **144**, 297, 1929.
4. ETHERIDGE, C. B., MYERS, D. B., and FULTON, M. N.: *Med. Papers Dedicated to Henry Christian*, Waverly Press, p. 223, 1936.
5. FÖLLING, A.: *Acta med. Scand.*, **71**, 221, 1929.
6. GAMBLE, J. L., BLACKFAN, K. D., and HAMILTON, B.: *J. Clin. Invest.*, **1**, 359, 1925.
7. GIBSON, J. G., JR., and EVELYN, K. A.: *J. Clin. Invest.*, **17**, 153, 1938.
8. KEITT, N. M., BANIER, C. W., and WHELAN, M.: *J. Am. Med. Assn.*, **85**, 799, 1925.
9. KEITT, N. M., and WHELAN, M.: *J. Clin. Invest.*, **3**, 149, 1926.
10. LOEB, R. F., ATCHELY, D. W., RICHARDS, D. W., JR., BENEDICT, E. M., and DRISCOLD, M. E.: *J. Clin. Invest.*, **11**, 621, 1932.
11. LYONS, R. H., AVERY, N. L., and JACOBSON, S. D.: *Am. Heart J.*, **27**, 353, 1944.
12. LYONS, R. H., JACOBSON, S. D., and AVERY, N. L.: *Am. J. Med. Sci.*, **208**, 148, 1944.
13. LYONS, R. H., AVERY, N. L., and JACOBSON, S. D.: *Am. Heart J.*, **28**, 247, 1944.
14. MELLARS, R. C., MUNTMYLER, E., MAUTZ, F. R., and ABBOTT, W. E.: *J. Biol. Chem.*, **144**, 785, 1942.
15. SAXL, P., and ERLSBACHER, O.: *Wien. klin. Wchnschr.*, **42**, 36, 1929.
16. WARREN, J. V., MERRILL, A. J., and STEAD, E. A.: *J. Clin. Invest.*, **22**, 635, 1943.
17. WILEY, F. H., WILEY, L. L., and WALLER, D. S.: *J. Biol. Chem.*, **101**, 73, 1933.
18. WINTROBE, M. M.: *J. Lab. and Clin. Med.*, **17**, 899, 1932.

THE RELATION OF ARTERIAL PULSE-PRESSURE TO ARTERIOVENOUS OXYGEN DIFFERENCE, ESPECIALLY IN ARTERIAL HYPERTENSION

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PULSE-PRESSURE in the brachial artery is no longer regarded as even a rough measure of cardiac output. Nor can we assume that it gives information concerning what is happening in other arteries. Furthermore, arterial distensibility decreases and pulse-pressure increases as internal pressure is raised, although deviations due to this factor are small in the range of human blood pressures.⁹ Comparisons involving pulse-pressure from different individuals (varying in size of vessels, muscle masses, metabolic rates, etc.) taken under varying conditions of temperature, humidity, and so forth, would seem therefore, to have little justification.

In spite of these considerations, an attempt was made to correlate certain data obtained from a number of patients of both sexes suffering from a variety of diseases. In Figure 1 the arteriovenous oxygen differences have been plotted against the products of the pulse pressure multiplied by pulse rate ($PP \times PR$) as ascertained on the brachial artery. Venous blood was drawn from the median basilic vein, and arterial blood usually from the brachial or sometimes from the femoral artery. It will be seen that most of these cases fall within a curved area (AA), the mean of which is roughly represented by a curve (DD) such that, for any point on the curve, $(PP \times PR) \times (A-V O_2 \text{ diff.}) = K_1$, a constant. (The shaded area E represents the "normal" area.) (1)

The oxygen consumption of an arm at rest can be assumed to be constant and equal to the product of the volume of blood entering or leaving the arm per minute (V) and the volume of oxygen lost by

each 100 cc. of blood while traversing the arm, or,

$$V \times (A-V O_2 \text{ diff.}) = K_2 \quad (2)$$

If equation (1) above correctly expresses a general relationship between these two variables, it follows that V varies directly as, or is proportional to, $PP \times PR$. The latter can therefore be used as a fair clinical indication of blood flow through the arm.

On further inspection it was found: (a) that those cases falling in the lower portion of the "curved area," with circulatory stasis, are all, as might be expected, cases of cardiac disease (valvular disease, calcified pericarditis, emphysema), cancer, certain severe anemias, and so forth, (b) that those cases falling in the upper part of the "curved area," with a large pulse pressure and a rapid passage of blood through the tissues, are nearly all cases of arterial hypertension and certain other cases of anemia with low diastolic pressures, and (c) that those cases known to have a lowered basal metabolic rate fall to the left, and those with an increased BMR fall to the right of the "curved area." These cases are omitted from Figure 1.

Arterial Hypertension. Since the above results were published in 1941,⁴ we have attempted to use the graph in Figure 1, to throw light on certain aspects of the phenomena of arterial hypertension. We therefore examined an additional group of hypertensive patients, selecting those without symptoms of cardiac failure, who were, as a rule, attending hospital for some other disease, and in whom the hypertension was discovered only on routine examination. In all cases the diastolic pressure was 90 or more. Again, the results show

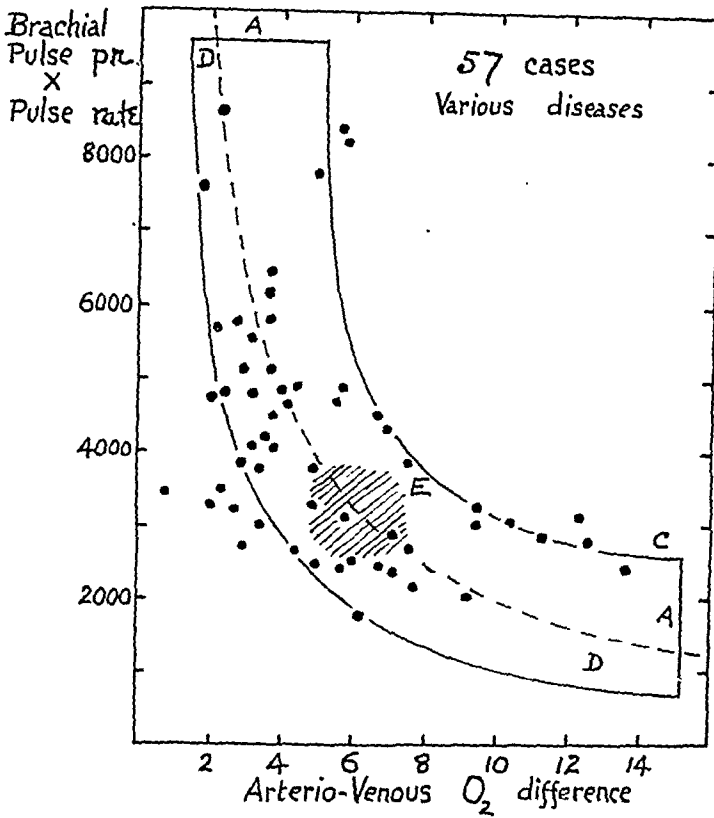


FIG. 1.

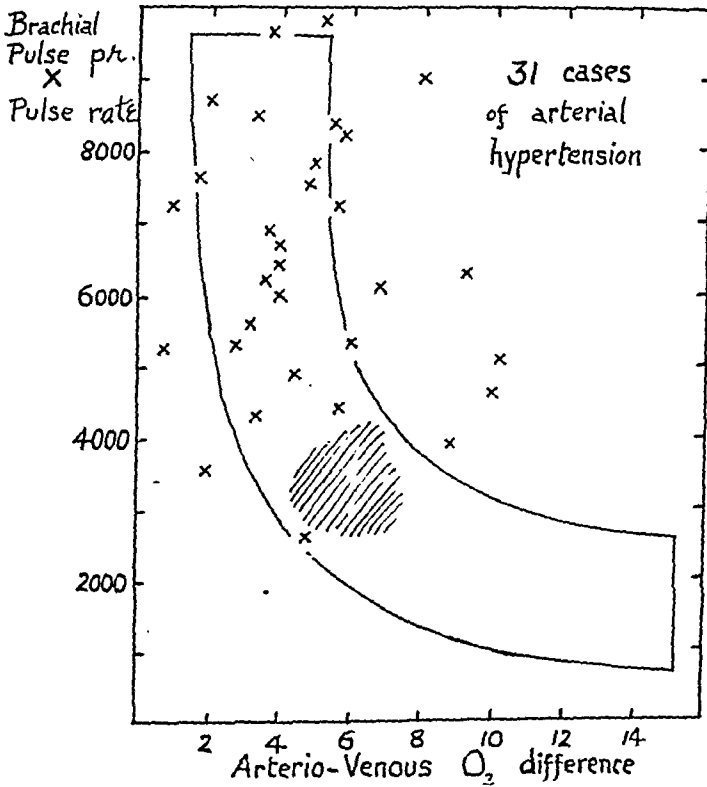


FIG. 2.

that, in general, these cases fall at the upper end, and in some cases to the right of, the "curved area" (Fig. 2).

Since these experiments seemed to offer the additional opportunity to investigate certain aspects of the old controversial question of the relation of blood chlorides to arterial hypertension, we also determined the arteriovenous whole blood chloride differences (Eisenman's method)⁷ for comparison with the arteriovenous oxygen differences (Fig. 3).

Since the cardiac output per minute in hypertensives is not increased (or if anything, even diminished),⁶ and the blood flow through the limb is increased it follows that the volume of blood flowing through the viscera must be diminished, *i. e.*, that general vasoconstriction is more marked in viscera than in limbs, and may even be absent in the limbs.

From these results it would seem that, instead of regarding variations in pulse-pressure as indications of similar variations

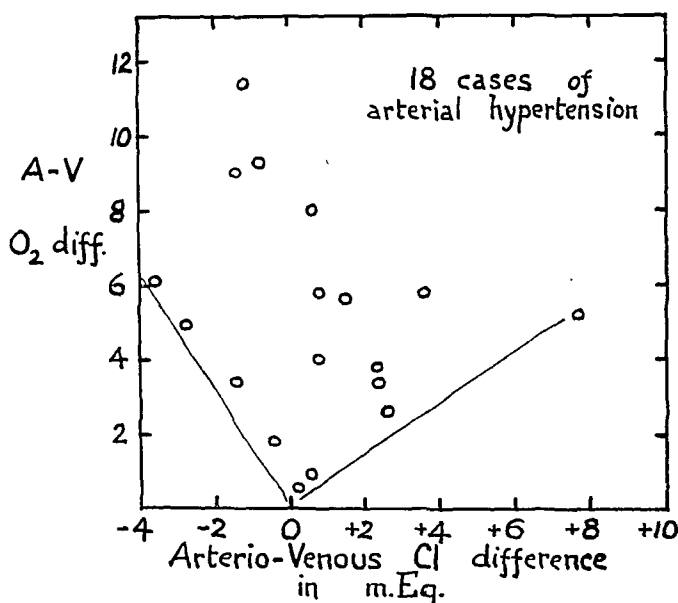


FIG. 3.

Discussion. (A) *Blood Flow in Limbs and Viscera.* It has often been assumed that, in arterial hypertension, the vasoconstriction more or less equally involves all of the peripheral arterioles, whether in limbs or in viscera. This conception was supported by the work of Prinzmetal and Wilson¹² and of Pickering¹¹ (using plethysmographic methods) which indicated that the blood flow through the arms was unchanged in hypertension. On the other hand Grant and Pearson,⁸ Abramson,¹ and Apperly and Cary⁴ (the last named using the method here described) showed an increased blood flow through the arms in hypertension. Grant⁸ and Abramson¹ further demonstrated that the same holds true for the calf of the leg.

in cardiac output, we should rather regard them as indicating the varying use of the limbs as a "blood shunt," *i. e.*, that the high pulse-pressure of hypertension and some anemias indicates that a larger (and the low pulse-pressure of circulatory failure a lower) proportion of the total blood volume is being shunted through the limbs, and possibly through all muscle masses. The value of such an arrangement for reciprocally varying muscular and visceral needs is of course obvious. It is of interest that epinephrine produces the same results.

It was remarked above that in the cases of those people known to have a high BMR, their points fell to the right of the "curved area," which indeed was to be

expected. As is well known, the BMR is also increased in cases where the heart has increased work to do, as in arterial hypertension, chronic valvular disease and many cases of severe anemia. At first sight therefore we might expect that many of our cases of hypertension would also fall to the right of the curve, or in other words, that the upper end of the "curved area" in Figure 2 would always be bent to the right. On further consideration, however, this displacement is not so clear. For if the higher BMR is due entirely to the increased cardiac work we would expect conditions in the arm to be unaffected and therefore the points on the graph to be scattered along the median curve DD. The fact, however, that many of the points representing these cases are displaced to the right of the curved area indicates, unexpectedly, that the oxygen consumption in the arm is also augmented and that probably the increased metabolism is general.

(B) *The Chlorides in Arterial Hypertension.* Until recent years there was much discussion and conflicting opinion concerning the work of Allen and Sherril,^{2,3} who demonstrated the common association of hyperchloremia (in venous blood) with arterial hypertension, and claimed good therapeutic results from salt deprivation. We also showed that, on the whole, the blood chloride was raised, but found that the chloride spread among the hypertensives considerably overlapped that of our normal subjects.⁵ Schmitt and Basse¹⁸ obtained the same results in chronic nephritis but, on the whole, contrary results in essential hypertension.

The results quoted above were obtained from venous blood. Now it is known that generally, with increasing blood stasis, as in cardiac failure even without edema, there is a loss of chloride from the blood into the tissues, and the venous blood chloride falls.¹⁰ Conversely, it might be expected that when the blood flow through the tissues increases above normal the venous blood chloride would be higher than normal. The increased blood flow

through the arm in essential hypertension might therefore possibly account for the generally increased blood chloride, as determined in venous blood from the arm. In that case the arteriovenous oxygen differences should have (a) a direct relationship with arteriovenous chloride differences and (b) an inverse relationship with venous blood chlorides.

Figure 3 shows that these simple relationships were not realized. It is true that when the A-V oxygen difference was very small, *i. e.*, a large blood flow through the arm, the A-V chloride difference was also small. The blood, in fact, was rushed through the tissues too rapidly to allow time for A-V differences to occur. As the A-V oxygen difference increased, however, the A-V chloride differences also increased, but in varying directions, some positively and some negatively.

These results obviously show that two or more factors, acting in opposite directions, are at work. Attempts to correlate these changes with pulse-pressure, diastolic pressure, or the ratio of the former to the latter, were fruitless. The final direction of the chloride shift during the passage of blood through the arms as the A-V oxygen difference increases (*i. e.* with increasing stasis), is probably the resultant of at least two forces: (a) with increasing stasis there is a rising capillary pressure and increased transudation of water and salts, including chlorides. Since the concentration of chlorides in plasma is greater than that in red cells, this means a loss of chlorides from the blood as a whole and hence a positively increasing A-V chloride difference. (b) With increasing stasis there is also increasing accumulation of carbon dioxide in the tissues, with consequent shift of chloride from tissues to capillary blood, and hence an increasingly negative A-V chloride difference. Whether the condition of the lungs or other organs determine which of these two factors will predominate is unknown. It would appear, however, from these and from our earlier studies,⁵ that there is no constant relationship between blood chlorides and arterial

hypertension, and that the factors governing the former are complex.

Conclusions. 1. Since pulse-pressure \times pulse rate \times arteriovenous oxygen difference in the arm of different subjects roughly equals a constant, PP \times PR is regarded as a fair index of blood flow entering the arm.

2. Since PP \times PR is increased and A-V O₂ difference is diminished in the limbs in arterial hypertension (in which total cardiac output is not increased), it follows that a larger proportion than normal of total blood flows through the limbs (and possibly all muscle masses), *i. e.*, peripheral vasoconstriction is absent or less marked in the limbs than in the splanchnic area. Hence the increasing

pulse-pressure commonly found with increasing hypertension.

3. In patients with high metabolic rates, the points on the graph are moved to the right of the normal curve, indicating an increased oxygen consumption in the arm. The fact that many cases involving increased cardiac work also move to the right shows that the increased metabolism in these cases is not due to increased cardiac work alone, but takes place in the arms also and is possibly a general condition.

4. It is suggested that the pulse-pressure serves as a rough but valuable indication of the reciprocally varying needs and blood supply of the viscera and muscular masses of the body.

5. No relation could be found between hypertension and blood chlorides.

We are indebted to Dr. W. B. Porter, Professor of Medicine, and to Drs. G. Watson James and Oscar Clarke, Assistant Residents in Medicine, for valuable help and advice.

REFERENCES

1. ABRAMSON, D. I.: Resting Peripheral Blood Flow in Hypertensive Subjects, *Proc. Soc. Exp. Biol. and Med.*, **45**, 127, 1940.
2. ALLEN, F. M.: Arterial Hypertension, *J. Am. Med. Assn.*, **74**, 652, 1920.
3. ALLEN, F. M., and SHERRIL, J. W.: The Treatment of Arterial Hypertension, *J. Metab. Res.*, **2**, 429, 1922.
4. APPERLY, F. L., and CARY, M. K.: Relation of Arterial Pulse-pressure to Arteriovenous Oxygen Difference, Especially in Arterial Hypertension, *Proc. Soc. Exp. Biol. and Med.*, **48**, 492, 1941.
5. APPERLY, F. L., and CARY, M. K.: Arterial Hypertension: The Site and Significance of High Chloride Content of Blood, *Am. J. Med. Sci.*, **194**, 352, 1937.
6. BURWELL, C. S., and SMITH, W. C.: The Output of the Heart in Patients With Abnormal Blood Pressures, *J. Clin. Invest.*, **7**, 1, 1929.
7. EISENMAN, A. J.: A Note on the Van Slyke Method for the Determination of Chlorides in Blood and Tissues, *J. Biol. Chem.*, **82**, 411, 1929.
8. GRANT, R. T., and PEARSON, R. S. M.: Blood Circulation in the Human Limb; Observations on the Differences Between the Proximal and Distal Parts and Remarks on the Regulation of Body Temperature, *Clin. Sci.*, **3**, 119, 1938.
9. HALLOCK, P., and BENSON, I. C.: Studies on the Elastic Properties of Human Aorta, *J. Clin. Invest.*, **16**, 595, 1937.
10. PETERS, J. P., BULGER, H. A., and EISENMAN, A. J.: Total Acid-base Equilibrium of Plasma in Health and Disease. VIII. Bicarbonate and Chloride in the Serum of Patients With Heart Failure, *J. Clin. Invest.*, **3**, 497, 1927.
11. PICKERING, G. W.: The Peripheral Resistance in Persistent Arterial Hypertension, *Clin. Sci.*, **2**, 209, 1936.
12. PRINZMETAL, M., and WILSON, C.: The Nature of the Peripheral Resistance in Arterial Hypertension With Special Reference to the Vaso-motor System, *J. Clin. Invest.*, **15**, 63, 1936.
13. SCHMITT, F., and BASSE, W.: Mineralaustausch-vorgänge zwischen Plasma und Erythrocyten beim Addison, *Arch. f. Exp. Path. u. Pharmacol.*, **181**, 581, 1936.

THE AGGLUTINATION REACTION FOR HEMOLYTIC STREPTOCOCCI IN RHEUMATOID ARTHRITIS; ITS SIGNIFICANCE IN DIAGNOSIS AND TREATMENT*

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It is rather remarkable that rheumatoid arthritis, which is obviously a systemic disease and one which can induce such marked changes in joint tissue, should be characterized by so few demonstrable changes in the physiology and chemistry of the body. This statement applies particularly to the various components of the blood and urine and even of the joint fluid. To be sure, the sedimentation rate is elevated in a very high percentage of cases, but so it is in many other systemic diseases; and a similar elevation is noted in all other inflammatory conditions of the joints. The frequently noted anemia and leukocytosis are equally non-specific and provide very little aid to an accurate diagnosis. The only really specific reaction so far described for rheumatoid arthritis is the streptococcal agglutination reaction. Agglutinins for the *Streptococcus hemolyticus* were first demonstrated in the serums of patients with rheumatoid arthritis in 1930 by Cecil, Nicholls and Stainsby,³ who showed that most of the attenuated hemolytic strains recovered from arthritic patients were agglutinable with rheumatoid serum, often in rather high dilutions. In a series of 103 cases of rheumatoid arthritis, 97 showed agglutination with the "typical strain" of streptococcus at a dilution of 1 to 640 or higher, while in a series of 50 normal controls the serum in every case failed to give a strong agglutination reaction. Nicholls and Stainsby²⁰ noted that hemolytic streptococci from other sources, such as scarlet fever and erysipelas, were often agglutinable with

arthritic serum. These results were confirmed by Dawson, Olmstead and Boots⁷ and many others. It has also been found that the serums of patients with rheumatoid arthritis frequently give a positive precipitation reaction with the protein fractions of *S. hemolyticus*.

Table 1 summarizes the results obtained by various investigators with respect to the incidence of specific agglutinins for the *S. hemolyticus* in the serums of rheumatoid patients.

The object of this investigation was to determine the present status of the streptococcal agglutination reaction in rheumatoid arthritis and to find out, if possible, the effect of gold therapy on this interesting phenomenon.

In this study we have investigated: (1) the optimal conditions under which the agglutination reaction against the hemolytic streptococcus should be carried out; (2) the incidence of streptococcal agglutinins in sera (a) of patients with typical rheumatoid arthritis of varying duration; (b) of patients with other joint diseases; (c) of patients suffering from streptococcal infections; (d) of normal controls; and (3) the incidence of streptococcal agglutinins in patients with rheumatoid arthritis before and after treatment with gold salts.

Material and Methods. Antistreptococcal rabbit sera were used for positive controls and in tests designed to study the optimal conditions of the reaction. The sera were prepared by repeated intravenous injections of rabbits with formalin-killed Group A hemolytic streptococci (strain AB13 or strain

* Aided by a grant from the John and Mary R. Markle Foundation, the Ophthalmological Foundation, and the Dazian Foundation for Medical Research, New York.

NY5). Only sera having an agglutinin titer for the homologous strain of at least 1 to 640 were employed.

For the study of human sera approximately 5 cc. of blood were withdrawn from a cubital vein and transferred into a sterile test tube. After retraction of the clot and short centrifugation, the clear supernatant serum was removed with a sterile capillary pipette and stored without preservative in the ice box until used. The sera were usually examined within 1 to 2 weeks after withdrawal.

addition of 0.2% formalin. Killed suspensions kept in the ice box at approximately + 4° C. can be used for 1 week.

Reaction. Five-tenths cc. quantities of serial dilutions of the sera in 0.9% saline solution from 1 to 10 to 1 to 2560 were mixed with 0.5 cc. quantities of the antigen, thus making final dilutions of the sera from 1 to 20 to 1 to 5120. All reactions were carried out in 10 × 75 mm. Pyrex test tubes.

Controls. The following controls were made: (1) antigen + saline; (2) serial dilutions of a normal serum of the same species

TABLE 1.—REVIEW OF LITERATURE (1930-1942) CONCERNING PRESENCE OF STREPTOCOCCAL AGGLUTININS IN THE BLOOD OF PATIENTS SUFFERING FROM RHEUMATOID ARTHRITIS

Author	No. of patients studied	% of positive reactions
Cecil, Nicholls and Stainsby ³	103	94.0
Nicholls and Stainsby ²⁰	110	93.6
Gray and Gowen ¹⁴	60	75.0
Dawson, Olmstead and Boots ⁷	206	55.0
Gray, Fendrick and Gowen ¹⁵	144	69-80
Ashworth ¹	65	89.2
Clawson, Wetherby, Hilbert and Hilleboe ⁵	60	59.5
Keefer, Myers and Oppel ¹⁸	22	54.5
Nicholls and Stainsby ²¹	613	45.0
Cox and Hill ⁶	41	71-81
Dawson, Olmstead and Jost ⁸	71	56.3
Wainwright ²³	51	54.9
Blair and Hallman ²	62	82.0
Gray, Bernhard and Gowen ¹⁶	200	70-76
McEwen, Bunim and Alexander ¹⁹	36	56.0
Goldie and Griffiths ¹³	28	89.0
Hartung, Davis, Steinbrocker and Straub ¹⁷	50	36.0
Short, Dienes and Bauer ²²	47	53.1
Ferry and Hunt ¹²	36	58.0

Antigen. Living and killed cultures of two strains of Group A hemolytic streptococci (AB13 and NY5) were used. The stock cultures of these strains were kept in 5% blood broth in the ice box and transferred every month.

Experiments With Living Cultures. Eighteen hour broth cultures were used; these were prepared by transferring 0.5 cc. quantities of stock culture into bottles containing 100 cc. of veal infusion broth.

Experiments With Killed Cultures. Eighteen hour broth cultures, prepared in the same manner as those for the experiments with living organisms, were centrifugalized for 30 minutes at 2000 r.p.m. and the sediment resuspended in an amount of 0.9% saline solution equal to one-half the volume of the original culture. The saline suspension of the organisms was then killed by heating for 1 hour in a water bath at 60° C. In some instances the cultures were killed by the

(human or rabbit) + antigen; (3) serial dilutions of a positive serum of the same species (human or rabbit) + antigen; (4) each serum to be tested + saline and (5) each control serum + saline. Only experiments in which Controls 1, 2, 4 and 5 were negative and Control 3 positive were considered acceptable.

Incubation Method. The serum-antigen mixtures were incubated for 2 hours at 56° C. and then kept overnight in the ice box at 4° C. Readings were made after refrigeration.

Centrifugation Method. The serum-antigen mixtures were immediately centrifugalized for 15 minutes at 2000 r.p.m. and readings made immediately thereafter. The reactions were read by daylight. Those in which flocculation was grossly visible after gentle tapping of the tubes were recorded as positive. The procedure was similar to that

previously described by one of the authors (deGara) in experiments with pneumococci.¹¹

Results. *Study of Optimal Conditions for the Detection of Streptococcal Agglutinins.* The agglutinin titers obtained with the incubation and centrifugation methods with living and killed antigens were compared, making use of an antistreptococcal rabbit serum, the serum from a patient with rheumatoid arthritis, and normal rabbit and human sera (Table 2).

reactions were found with sera from normal men or normal rabbits.

In order to determine what concentration of antigen would give optimal reactions with the serum agglutinins over a wide range of dilutions, killed suspensions were prepared from cultures containing from 50 million to 300 million organisms per cc. The various suspensions were then tested with a known potent antistreptococcal rabbit serum (Table 3).

TABLE 2.—COMPARISON OF INCUBATION AND CENTRIFUGATION METHODS FOR DETECTION OF AGGLUTININS WITH HEMOLYTIC STREPTOCOCCI (STRAIN AB13) IN SERA OF RABBITS AND MEN

Serum	Antigen	Method	Agglutination titer
Immune rabbit	Living culture	Incubation	1:320
	Killed culture	Incubation	1:320
	Killed culture	Centrifugation	1:2560
Normal rabbit	Living culture	Incubation	Neg.
	Killed culture	Incubation	Neg.
	Killed culture	Centrifugation	Neg.
Patient with rheumatoid arthritis .	Living culture	Incubation	1:160
	Killed culture	Incubation	1:160
	Killed culture	Centrifugation	1:640
Normal human	Living culture	Incubation	Neg.
	Killed culture	Incubation	Neg.
	Killed culture	Centrifugation	Neg.

TABLE 3.—RELATION OF DENSITY OF STREPTOCOCCAL SUSPENSION TO DETECTION OF AGGLUTININS IN ANTISTREPTOCOCCAL RABBIT SERUM

Antigen: AB13 saline suspension (killed at 60° C. for 60 minutes).

Density (organisms per cc.)	Agglutination* by dilution of antistreptococcal rabbit serum of:								
	1:20	1:40	1:80	1:160	1:320	1:640	1:1280	1:2560	1:5120
300,000,000	+++	+++	+++	+++	+++	++	+	+	-
200,000,000	+++	+++	+++	+++	++	++	+	+	-
150,000,000	+++	+++	+++	+++	++	++	+	+	-
100,000,000	++	+++	+++	+++	++	++	+	-	-
75,000,000	++	++	++	++	+	+	-	-	-
50,000,000	-	+	++	++	+	-	-	-	-

* - means negative. + means small clumps, supernate turbid. ++ means small clumps, supernate clear. +++ means large clumps or firm disk, supernate clear.

The titers obtained by the incubation method were the same, whether living or killed cultures were used as antigens. The titers yielded by the centrifugation method were definitely higher than those by the incubation method (Table 2). Since the same killed culture was employed with both methods, the results are comparable and indicate that the centrifugation provides a more sensitive method for the detection of streptococcal agglutinins than does the incubation method. No positive

With a weak bacterial suspension containing approximately 50 million organisms per cc., reactions were obtained only in serum dilutions up to 1 to 320, and there was a definite inhibition of the reaction in the zone of antibody excess. The range of the reaction with denser suspensions, containing 75 million or 100 million streptococci per cc., increased in width, but the full range was obtained only with an antigen prepared from a culture containing at least 150 million

organisms per cc. (Table 3). Since 18 hour broth cultures of the strains used contained approximately 75 to 100 million organisms per cc., the sediment of these cultures was resuspended in an amount of saline equal to one-half the amount of the original broth culture; then the saline suspension was immediately killed by heat, as described above. These suspensions contained approximately 150 to 200 million organisms per cc. and were used for the reactions with sera from men or from animals.

of streptococcal agglutinins in the sera obtained from 480 persons. The criteria for identification of rheumatoid arthritis were the following:

Rheumatoid Arthritis. (1) Presence of fusiform fingers, (2) multiple joint involvement, (3) presence of subcutaneous nodules, (4) typical Roentgen ray appearance of the bones and joints, and (5) acceleration of the sedimentation rate of the red blood cells. Only cases that presented at least 3 of these 5 symptoms were included in our series. Patients who had had rheu-

TABLE 4.—INCIDENCE OF STREPTOCOCCAL AGGLUTININS IN HUMAN SERA UNDER NORMAL AND PATHOLOGIC CONDITIONS

Clinical diagnosis	No. of cases	Cases having agglutinins in a serum dilution of 1:160 or higher	
		No.	%
Rheumatoid arthritis:			
"Late"	190	126	66.3
"Early"	78	36	46.1
Total	268	162	60.4
Subacute infectious arthritis	6	3	50.0
Ankylosing spondylitis (Marie-Strümpell)	16	1	6.2
Osteoarthritis	95	1	1.0
Gonococcal arthritis	4	0	0.0
Various other joint diseases	48	0	0.0
Rheumatic fever	8	0	0.0
Scarlet fever	8	2	25.0
Normal controls	27	0	0.0
Total	480		

The agglutinin titer for 2 different strains of hemolytic streptococci (AB13 and NY5) was studied in 110 sera from patients with rheumatoid arthritis. It was found that 73 of them (66%) had approximately the same titer for both strains, while differences were noted in the remaining 37 sera (34%). Of these, 19 showed a higher titer for strain AB13, and 18 contained more agglutinins for strain NY5.

The centrifugation and incubation methods were simultaneously carried out on 110 sera from patients with rheumatoid arthritis. Of these 66 (60%) gave approximately the same results with both methods, while in the remaining 44 instances (40%) higher titers were observed with the centrifugation method.

Incidence of Streptococcal Agglutinins in Human Sera. Table 4 shows the incidence

matoid arthritis for less than 1 year were classified as early, those with a rheumatoid history of more than 1 year, as late cases.

Subacute Infectious Arthritis. In this group cases of arthritis following acute infectious diseases were included.

Various Other Joint Diseases. This group comprises patients suffering from intermittent hydroarthrosis, menopausal arthrosis, gouty arthritis, and various joint conditions not included in the other groups.

The criteria used for the diagnoses of gonococcal arthritis, ankylosing spondylitis (Marie-Strümpell), osteoarthritis, and scarlet fever were those generally employed. A few cases of rheumatic fever with rheumatic carditis were also included.

Normal Controls. Sera from healthy individuals of various ages and sexes that

had no subjective or objective symptoms of arthritis were used.

Table 4 shows that 60.4 % of the patients with rheumatoid arthritis had agglutinins for hemolytic streptococci in a serum dilution of at least 1 to 160. There was, however, a considerable difference between the sera from late cases, 66.3 % of which contained agglutinins, and those from early cases, where they were found in only 46.1 %. Of the 6 sera from patients with subacute infectious arthritis, 3 (50 %) contained antistreptococcal agglutinins; 2 of 8 sera from persons with scarlet fever (25 %) agglutinated hemolytic streptococci in a titer of 1 to 160 or higher. One of 16 patients with ankylosing spondylitis (Marie-Strümpell) who also suffered from rheumatoid arthritis had agglutinins for hemolytic streptococci in his serum. Of 95 patients with osteoarthritis, only 1 had agglutinins for streptococci. No agglutinins were found in the remaining 60 sera from patients suffering with gonococcal arthritis, various other joint diseases, or with rheumatic fever, and none were present in those of the 27 normal controls.

Degree of severity*	Total No. examined	Cases with agglutinins	
		No.	%
Mild	82	38	46.3
Moderately severe	145	97	66.8
Severe	41	27	65.8
Total	268	162	60.4

* Mild cases, ambulant. These patients were still able to work every day, and had only a moderate degree of swelling and pain in several joints, including usually 2 or 3 fingers.

Moderately severe cases, mostly ambulant. These patients were usually only partly incapacitated and could do certain kinds of work. They invariably presented a multiple arthritis with well-established changes in the hands, wrists, knees and other joints.

Severe cases, only partially ambulant, and capable of performing little or no work.

Relation of Streptococcal Agglutinins to Severity of Rheumatoid Arthritis. The relationship of the severity of rheumatoid arthritis to serum agglutinins for hemolytic streptococci is presented in the following tabulation. The degree of severity (mild, moderate, severe) was established accord-

ing to the criteria given by Cecil, Kammerer and dePrume.⁴

The majority of our 268 patients suffered from moderately severe rheumatoid arthritis. The percentage having agglutinins for streptococci was practically identical in moderately severe and severe cases; it was lower in those classified as mild.

Relationship of Streptococcal Agglutinins in Rheumatoid Arthritis to Presence of Subcutaneous Nodules and to Psoriatic Arthritis. Subcutaneous nodules were found in 25 of the 268 patients with rheumatoid arthritis (9 %). Streptococcal agglutinins were present in the serum of 20 of them (80 %).

Psoriasis (arthritis psoriatica) was present in 15 of the 268 rheumatoid patients (5 %). Of these, 10 had serum agglutinins for hemolytic streptococci (66.6 %).

Relationship of Streptococcal Agglutinins to Sedimentation Rate of Erythrocytes. The sedimentation rate of the red blood cells, as determined by the Rourke and Ernstone method, was studied in 431 patients.

Table 5 shows that in patients with rheumatoid arthritis an elevated sedimentation rate was found more frequently than agglutinins for hemolytic streptococci. However, an elevated sedimentation rate was also present in 22.8 % of "normal" controls and in 34 % of persons affected with joint diseases other than rheumatoid arthritis, none of whom had agglutinins for hemolytic streptococci. These results indicate that a positive agglutination reaction for hemolytic streptococci is much more specific for rheumatoid arthritis than an elevation of the sedimentation rate.

Effect of Gold Treatment on the Streptococcal Agglutination Reaction. The agglutinin titer for hemolytic streptococci before and after treatment with gold salts was studied in 37 patients suffering from rheumatoid arthritis of varying severity and duration. The gold salt administered was either gold sodium thiomalate (myochrysin) or aurothioglucose (solganal-B oleosum).

The agglutination reaction remained positive in 17 patients, and became negative in the remaining 20, either during treatment with gold salts or after its completion. There was no relationship between the type or amount of gold salts given and change in the agglutinin titer; in some instances the agglutinins disappeared after 300 to 500 mg. of gold salts had been administered, while in others the reaction remained positive after a total gold dosage as high as 13.45 gm. There was, however, some relationship between the changes in the agglutinin titer and the severity of rheumatoid arthritis, its duration and the results achieved with gold therapy.

which the agglutinin titer had become negative was found in mild and early forms of the disease and in those who had shown the most favorable response to gold therapy, an attempt was made to determine if the results obtained could be considered as "specific" for the treatment given. Accordingly, 24 cases who had not received gold therapy were analyzed. These patients received various forms of treatment, such as vaccine therapy, bee venom or physiotherapy. The results in this group were almost identical with those of patients who had received injections of gold salts. Seventy to 80% of the mild and early cases, as well as of those

TABLE 5.—COMPARISON OF TITERS OF STREPTOCOCCAL AGGLUTININS AND SEDIMENTATION RATE OF ERYTHROCYTES UNDER NORMAL AND PATHOLOGIC CONDITIONS

Clinical diagnosis	No. of cases	% having agglutinins in serum dilution of 1:160 or higher	% with C.S.I.* over 0.5
Rheumatoid arthritis:			
"Late"	175	65.6	90.9
"Early"	76	46.1	76.4
Total	251	59.7	86.5
Subacute infectious arthritis	6	50.0	83.4
Ankylosing spondylitis (Marie-Strümpell)	15	6.6	86.7
Osteoarthritis	86	1.1	42.4
Various other joint diseases	44	0.0	34.1
Rheumatic fever	7	0.0	85.8
Normal controls	22	0.0	22.8
Total	431		

* C.S.I. = Corrected sedimentation index.

Of the 37 gold cases studied, 7 had a mild form of rheumatoid arthritis and in 6 of them the agglutinin titer became negative during gold treatment (86%); but of the remaining 30 moderately severe or severe cases only 14 lost their positive agglutination reaction (46%). Similarly, 10 of the 13 early cases (77%), but only 10 of the 24 late cases (41%), became negative on gold therapy. Finally, in 12 of 16 patients (75%) who showed remission or marked improvement the agglutination reaction became negative, while only 8 of 21 (38%) who showed little or no clinical improvement during treatment with gold salts lost the agglutinins for hemolytic streptococci.

Since the highest percentage of cases in

showing marked improvement, lost their agglutinins; but in only 30 to 40% of patients with severe or late arthritis, and of those with little or no clinical improvement did the agglutination reaction become negative.

Discussion. The results obtained in this study indicate that the centrifugation method offers optimal conditions for the detection of streptococcal agglutinins in the serums of men and of animals. This procedure permits the titration of the antibody content within a few hours after the withdrawal of the blood, and it yields a sharp end reaction even in high dilutions of serum. This is in agreement with similar observations on the detection of pneumococcal agglutinins.¹¹

Living streptococci and those killed by heating or by the addition of formalin were agglutinated equally well. This corroborates the observations of Dawson, Olmstead and Boots.⁹

In order to avoid non-specific agglutination reactions so frequently observed at lower temperatures, the agglutination tests with living streptococci were always done at 56° C. (incubation method); with the centrifugation method the reaction with the heat-killed antigen was carried out at room temperature (24 to 26° C.).

In studying the optimal conditions of the reaction it was found that the concentration of the antigen must be sufficient to obtain positive reactions over a wide range and at the same time avoid the occurrence of inhibition zones. This is in agreement with the observations by Dean and Webb.¹⁰

In this series the incidence of streptococcal agglutinins in the serum of 268 patients with rheumatoid arthritis was 60.4%. The incidence was higher (66.3%) in late cases than it was in early cases (46.1%). These results agree with previous reports by Dawson *et al.*⁹ and by Short *et al.*,²² who also found that streptococcal agglutinins occurred in early cases approximately one-half as frequently as in late cases.

Streptococcal agglutinins were found in 30% of cases of subacute infectious arthritis and in 25% of patients with scarlet fever. The incidence of streptococcal agglutinins was very low or nil in the other clinical groups, which included osteoarthritis, ankylosing spondylitis, rheumatic fever, and normal controls. These results are in agreement with those obtained by previous investigators.

A definite relationship was found between the incidence of the agglutinins in rheumatoid arthritis and the severity of the disease. Mild cases had agglutinins in the serum in 46.3%; this figure increased to approximately 66% in more severely affected patients. These results are in accord with the observations of Nicholls and Stainsby,²¹ who reported that the

average agglutinin titers in patients with advanced joint lesions were higher than in those with less involvement. The incidence of streptococcal agglutinins was particularly high (80%) in patients who had subcutaneous nodules, the presence of which usually indicates a rather severe form of rheumatoid arthritis.

There was some relationship between the rate of sedimentation of the red blood cells and the incidence of serum agglutinins for hemolytic streptococci in rheumatoid arthritis, but this correlation was not absolute; frequently the sedimentation rate was elevated and no agglutinins were found; in other instances agglutinins were detected while the sedimentation rate was normal. Similar observations have been made by Dawson, Olmstead and Boots,⁹ by Keefer, Myers and Oppel,¹⁸ by Blair and Hallman² and by Short, Dienes, and Bauer.²² High sedimentation rates were also observed in various other joint diseases and even in normal controls. This indicates that the agglutination reaction for streptococci is more specific for rheumatoid arthritis than the sedimentation rate of the erythrocytes.

Treatment with gold salts of patients with rheumatoid arthritis was frequently followed by diminution or disappearance of the agglutinins for hemolytic streptococci. This was noted particularly in patients who showed a good response to gold therapy. However, the reduction of the antibody titer was not limited to patients who had received gold therapy. Similar observations were made in patients who had shown favorable response to other forms of therapy. On the other hand, gold did not interfere with the production or with the persistence of streptococcal agglutinins. It may be concluded, therefore, that gold does not exert a direct influence upon the agglutinins. In other words, gold does not affect directly the production of agglutinins, nor does it play an immediate rôle in their disappearance except in those cases where remission or great improvement occurs.

Summary and Conclusions. 1. Optimal conditions for the detection of agglutinins for Group A hemolytic streptococci in the serum of patients suffering from rheumatoid arthritis have been studied. The most rapid and satisfactory reactions have been obtained by centrifugation of the test tubes containing the antigen-antibody mixtures at room temperature.

2. The incidence of streptococcal agglutinins in 268 patients with rheumatoid arthritis was 60.4%. It was higher in late cases (66.3%) than in early cases (46.1%). In both early and late cases, the percentage of positive reactions was higher in the severe cases than in the mild ones.

3. In patients with rheumatoid arthritis there was a rough parallelism between the percentage of positive agglutination reactions for hemolytic streptococci and the sedimentation rate of erythrocytes.

4. Treatment with gold salts did not exert any specific influence on agglutinins for hemolytic streptococci. Diminution or complete disappearance of the agglutinins was observed in a majority of rheumatoid patients who showed a remission or marked improvement, whether they received gold therapy or some other form of treatment.

REFERENCES

1. ASHWORTH, O. O.: *Virginia Med. Monthly*, **59**, 452, 1932.
2. BLAIR, J. E., and HALLMAN, F. A.: *J. Clin. Invest.*, **14**, 505, 1935.
3. CECIL, R. L., NICHOLLS, E. E., and STAINSBY, W. J.: *Sci. Proc.*, 30th Ann. Meet. Am. Assn. Path. and Bact., New York, 1930; *Am. J. Path.*, **6**, 619, 1930; *Trans. Am. Assn. Phys.*, **45**, 210, 1930; *Am. J. Med. Sci.*, **181**, 12, 1931.
4. CECIL, R. L., KAMMERER, W. H., and DE PRUME, F. J.: *Ann. Int. Med.*, **16**, 811, 1942.
5. CLAWSON, B. J., WETHERBY, M., HILBERT, E. H., and HILLEBOE, H. E.: *Am. J. Med. Sci.*, **184**, 758, 1932.
6. COX, K. E., and HILL, D. F.: *Arch. Int. Med.*, **54**, 27, 1934.
7. DAWSON, M. H., OLMSTEAD, M., and BOOTS, R. H.: *Proc. Soc. Exp. Biol. and Med.*, **28**, 421, 1931; *J. Immunol.*, **23**, 187, 1932.
8. DAWSON, M. H., OLMSTEAD, M., and JOST, E. L.: *J. Immunol.*, **27**, 355, 1934.
9. DAWSON, M. H., OLMSTEAD, M., and BOOTS, R. H.: *J. Immunol.*, **23**, 205, 1932.
10. DEAN, H. R., and WEBB, R. A.: *J. Path. and Bact.*, **29**, 473, 1926.
11. DEGARA, P. F.: *Science*, **90**, 378, 1939.
12. FERRY, J. L., and HUNT, L. W.: *J. Lab. and Clin. Med.*, **27**, 705, 1942.
13. GOLDIE, W., and GRIFFITHS, G. J.: *Brit. Med. J.*, **2**, 755, 1936.
14. GRAY, J. W., and GOWEN, C. H.: *Am. J. Med. Sci.*, **182**, 682, 1931.
15. GRAY, J. W., FENDRICK, E., and GOWEN, C. H.: *Texas State J. Med.*, **28**, 317, 1932.
16. GRAY, J. W., BERNHARD, W. G., and GOWEN, C. H.: *Am. J. Clin. Path.*, **5**, 489, 1935.
17. HARTUNG, E. F., DAVIS, J. S., STEINBROCKER, O., and STRAUB, M. E.: *J. Am. Med. Assn.*, **106**, 1448, 1936.
18. KEEFER, C. S., MYERS, W. K., and OPPEL, T. W.: *J. Clin. Invest.*, **12**, 267, 1933.
19. McEWEN, C., BUNIM, J. J., and ALEXANDER, R. C.: *J. Lab. and Clin. Med.*, **21**, 465, 1936.
20. NICHOLLS, E. E., and STAINSBY, W. J.: *J. Clin. Invest.*, **10**, 323, 1931; *J. Am. Med. Assn.*, **95**, 1146, 1931.
21. NICHOLLS, E. E., and STAINSBY, W. J.: *J. Clin. Invest.*, **12**, 505, 1933.
22. SHORT, C. L., DIENES, L., and BAUER, W.: *J. Am. Med. Assn.*, **108**, 2087, 1937.
23. WAINWRIGHT, C. W.: *J. Am. Med. Assn.*, **103**, 1357, 1934; *Bull. Johns Hopkins Hosp.*, **61**, 358, 1937.

PROGRESS OF MEDICAL SCIENCE

DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

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TUMORS OF THE SKIN

PART I.—A REVIEW OF RECENT LITERATURE,*

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THE skin, with the exception of the eye, is unique in that its exposed position subjects it to numerous hazards of the environment and also because its lesions are easily accessible for study and treatment. Failure to eradicate cutaneous neoplasm, with the exception of malignant melanoma, is usually the result of improper therapy or neglect by the patient or his physician to start treatment promptly. On the other hand, because of the various anatomic structures in the skin, the new growths and nevi are of many types and when more than one structure proliferates simultaneously, the result is a picture of great complexity. In epithelioma alone, tumors may be derived from the surface epiderm, the appendages (hair follicle, sebaceous gland, sweat gland and nail bed) and abnormal proliferation. About 18 years ago Weidman³²⁴ very ably summarized histologic evidence illustrating the capacity of human epiderm (developed perhaps phylogenetically) to regenerate so vigorously that it may simulate cancer. We do not intend to review all the factors involved in the development of benign and

malignant cutaneous tumors, but shall present a proposed classification of the numerous neoplastic (and some nevic) lesions of the skin and a discussion of the recent advances in the knowledge of the character and pathogenesis of a number of the tumors of the skin.

In a survey of this sort a certain amount of imbalance in presentation is inevitable. Lesions with clear-cut pathogenesis may receive little attention although, from the clinical standpoint, they are relatively more important if only because of their numerical incidence. On the other hand, rare but little understood entities may receive more attention than their rare occurrence would seem to merit. In any event, our intention is to present sufficient of the more informative literary references for one to have a convenient basis from which to launch further study.

Certain authors have contributed widely to our knowledge of cutaneous tumors. Their names will appear frequently in connection with their individual contributions.

Pomeroy²³⁴ has offered a classification of tumors which has the endorsement of

* The second part of this review, together with the references for both parts, will appear as the Progress article for this department in the October issue.

Ewing. The section on Cutaneous Tumors is herewith presented not as an entirely acceptable codification but to indicate graphically the extensive scope of the subject.

Tumors of Skin. The nomenclature of skin tumors is the result of an independent evolution and does not conform with the broader views of the nature of tumors recognized in the field of general pathology. To bring the nomenclature of skin tumors in closer accord with the general nomenclature of tumors, the following outline is suggested:

I. EPITHELIAL TUMORS.

A. *Benign Tumor.*

1. Papilloma.
2. Sebaceous adenoma.
3. Sweat gland adenoma.
4. Epidermoid cyst ("implantation cyst," usually traumatic, may be congenital) (Mason).
5. Dermoid cyst.
6. Sebaceous cyst.
7. Sweat gland cyst.

B. *Malignant Tumor.*

1. Basal cell carcinoma.
 - (a) Common basal cell carcinoma.

1. Proliferative type.
2. Destructive type (rodent ulcer).

- (b) Epithelioma adenoides cysticum of Brooke (probable origin in hair follicle or sebaceous gland).

This should be distinguished from adenoid cystic carcinoma (Spies); which may be cutaneous or non-cutaneous, and in the latter situation is usually malignant.

- (c) Cylindroma (a nevus arising from embryonal rest).

2. Squamous cell carcinoma.

- (a) Well differentiated.
- (b) Partially differentiated.
- (c) Undifferentiated.

3. Mixed basal and squamous cell carcinoma.

4. So-called "precancerous" dermatoses.

For many investigators who believe that they have seen

Bowen's and Paget's disease begin as true cancer cells, these affections should be classified as cancer (McCarthy).

- (a) Paget's disease (occasionally in regions other than the nipple).

- (b) Bowen's disease (dyskeratosis, intracellular edema, numerous mitotic figures, and giant cells).

C. *Secondary Tumor.*

Carcinoma of breast and stomach are the most common primary tumors (Willis).

II. CONNECTIVE TISSUE TUMORS.

A. *Benign Tumor.*

1. Fibroma (including keloid, which is tentatively regarded as neoplasm by most investigators).

Histiocytoma can usually be differentiated from fibroma only by vital staining with colloidal iron (Senear and Caro).

2. Myxoma.

3. Lipoma.

4. Xanthoma.

5. Neurofibroma.

The majority of cutaneous fibromas are now known to originate in the perineurium or the interstitial tissue of the peripheral nerves, and are therefore called "neurofibromas" (Andrews).

6. Hemangioma (clinically many sub-types: "nevus" flammeus, "nevus" vasculosus, angioma cavernosum and "nevus" araneus).

7. Lymphangioma.

8. Hemangio-endothelioma.

9. Lymphangio-endothelioma.

B. *Malignant Tumor.*

1. Spindle cell sarcoma.

2. Fibrosarcoma.

3. Liposarcoma.

4. Neurogenic sarcoma.

5. Hemangio-endothelial sarcoma.

6. Lymphangio-endothelial sarcoma.

7. Kaposi's disease (question as to whether sarcoma or not).

C. *Secondary Tumor.*

1. Sarcoma (sarcoma of bone and lymphosarcoma may metastasize to the skin [Willis]).

2. Myeloid leukemia (leukosis).
3. Lymphoid leukemia (leukosis).
4. Hodgkin's disease.
5. Mycosis fungoides (if any case is definitely shown to be a cutaneous manifestation of Hodgkin's disease or of lymphosarcoma, it should be so named).

III. TUMORS OF THE PIGMENT-FORMING TISSUES.

It is quite generally accepted that the nevus cell is the parent cell of the melanoma, but the origin of the nevus cells is still a controversial question. In both the benign and malignant forms of tumors arising from pigment-forming tissues, the amount of pigment is extremely variable. The designation of a tumor as a nevus or melanoma is dependent upon the type of cell rather than upon the presence of pigment.

A. Benign Tumor.

1. Nevus (there are many varieties, including pigmented and non-pigmented, angiomatous, hairy, fibrous and papilliferous forms).

B. Malignant Tumor.

Malignant melanoma or melanoblastoma.

- C. Secondary Tumor (malignant melanoma may metastasize to the skin [Willis]).

IV. GLOMUS TUMOR.

Neuromyo-arterial Tumor.

This is most common in the nail bed but may be found in other locations. It was formerly diagnosed as angiosarcoma, perithelioma or painful subcutaneous tubercle.

Any classification of cutaneous tumors is limited and not satisfactory because of our imperfect knowledge of the nature of many of the lesions. This classification contains tumors under headings, as well as comments regarding the nature of some of the lesions, which are not acceptable to all. In addition, there are certain omissions such as mixed tumor, for example. In this review special attention will be paid to some of the epithelial tumors, benign and malignant, to some of the connective tissue tumors and "pigment-forming tissue tumors," but we will not

consider the tumors often spoken of as the lymphoblastomas.

Tumors of the Sebaceous Glands.

Tumors of the fat glands of the skin are either benign or malignant. Benign tumor-like enlargements of the sebaceous glands have a histologic appearance which may not differ appreciably from that of the normal glands. There is considerable confusion and difference of opinion relative to the evaluation of benign neoplastic growths of the sebaceous glands just as is the case in connection with the various glandular structures throughout the body. Woolhandler and Becker³⁴⁰ in a valuable contribution classified their cases as adenoma sebaceum (Balzer); adenoma sebaceum (Pringle); acquired (senile) adenoma sebaceum; keratotic adenoma sebaceum; nævus sebaceus; nævus pigmentosus et sebaceous. There are other modifications of sebaceous gland growths and recently Arnold¹³³ presented the case of a linear unilateral lesion in which the sweat and sebaceous glands were larger and more actively secreting than those in the surrounding skin which he called *nævus seborrhæicus et sudoriferus*. Warren and Warvi³²² classify circumscribed lesions according to their clinical characteristics: (a) those occurring in old age; (b) those appearing at birth and at puberty; (c) those associated with other cutaneous and visceral abnormalities forming the syndrome of Pringle's disease.

There is no clear-cut histologic distinction between adenoma; hyperplasia and hypertrophy of the sebaceous gland. In fact, there are some authors who feel that adenoma is rarely a definitive morphologic entity. The abnormality is chiefly one of increase in age, number and location of glands "with minor aberrations such as absence or atrophy or basal cells, variations in the tendency for the central cells to degenerate, or absence of ducts. Atrophy of the lesions is not uncommon; some may become fibrotic; others may entirely disappear" (Warren and Warvi).

Although there are hyperplastic and hypertrophic changes in the sebaceous

glands as a result of chronic irritation (rhinophyma), these can hardly be classed as neoplastic.

Senile sebaceous adenoma ("Caspary's sebaceous adenoma") is the name employed for a relatively common cutaneous lesion, appearing on the face of seborrheic persons after puberty. The fully developed typical lesions are yellowish, irregularly round, flat-topped, frequently umbilicated papules. They are usually found on the forehead and nose but may occur elsewhere on the face. They may be single or multiple. Nomland^{212a} noted that they varied from less than 12 to more than 50 in number. Microscopically the chief change is hyperplasia of the sebaceous gland. There is usually an associated dermatitis of the involutional senile type. The exact nosologic position of this tumor is unsettled. Woolhandler and Becker in their review concluded that there is little support in the literature for the concept of senile sebaceous adenoma. Gilman⁹⁸ objected to the designation of the lesions as either nevi or adenomas. He pointed out that the glands composing the tumors are normal except for their complexity and size, that their arrangement is orderly and that they are all connected to follicles. He proposed the name adenomatoid sebaceous hyperplasia and believed that *Demodex folliculorum*, as a source of chronic irritation, was responsible for the process. The cause of the condition is still undetermined. Woolhandler and Becker, from their studies, believe a tumor is nothing more than simple adenomatosis (hyperplasia) and an acceptable designation for it is acquired sebaceous adenomatosis.

Adenoma Sebaceum (Balzer). Balzer and Menetrier¹⁹ were the first to use the term adenoma sebaceum for a process consisting of multiple tumors symmetrically distributed on the face, neck and scalp which appeared before puberty and continued to develop until the time of observation. Clinically, the lesions were yellow to pink discrete papules with white points resembling milia on their surfaces. Micro-

scopically the lesions contained cellular nests with a tendency toward lobular arrangement and cystic structure. Some of these lobules were connected with normal sebaceous glands. The cells constituting the tumor masses resembled those of the basal cell layer of the sebaceous alveoli, which in general did not undergo normal fatty changes. Around many of the cysts a gradual transition from the ordinary tumor cells resembling more closely those seen in the centers of normal sebaceous glands were observed. Balzer and Menetrier concluded that the tumors were true adenomas originating in the pilosebaceous apparatus and the cyst contained sebaceous material. Balzer and Grandhomme¹⁸ presented an analogous case in 1886. Since these reports, other cases purporting to be examples of the Balzer type of adenoma sebaceum have appeared in the literature. As a result of the various contributions three schools of thought have emerged as regards the nosologic position of this dermatosis: (1) it is a sub-variety of Pringle's sebaceous adenomas, the tumors being relatively avascular; (2) it is a sub-variety of Pringle's adenoma sebaceum with the lesions showing changes in the hair follicles; (3) it is epithelioma adenoides cysticum, a variety of multiple benign cystic epithelioma. Woolhandler and Becker consider the first two of these as untenable and subscribe to the idea that adenoma (Balzer) belongs in the group of multiple benign cystic epithelioma (cf. Ingels¹³²).

Adenoma Sebaceum (Pringle). Otherwise known as tuberous sclerosis and epiloia, Pringle's adenoma sebaceum, is a syndrome represented by various combinations of cutaneous tumors, visceral tumors, tuberous sclerosis, epilepsy and mental deterioration. The classical picture occurs in the syndrome known as epiloia recently described in detail by Butterworth and Wilson,⁴⁶ Good and Garb,¹⁰⁴ and Noon and Williams.²¹³ In this state which may occur in from 0.1 to 0.5% of the population of United States institutions for epileptics and feeble-minded (Noon and

Williams), three cardinal features are present: adenoma sebaceum, epilepsy and mental deterioration, with or without visceral tumors.

Description of the cutaneous lesions in the Pringle type of adenoma sebaceum is given by Woolhandler and Becker as follows:

They "occur invariably on the face, especially in the center, or so-called rosacea area, namely, the forehead, cheeks, nose and chin. They are always bilateral and roughly symmetric and vary considerably in number. They are most numerous in the nasolabial folds and on the adjoining part of the cheeks and nose. The lesions are papules or nodules, varying in size from that of a pinhead to that of a bean. Coalescence may occasionally occur, but as a rule the tumors are discrete. Their color varies from that of the normal skin to yellowish white, yellowish or brownish red, the color representing roughly the predominant tissue constituting the tumor. Telangiectases are a common accompaniment, occurring on the surface of the lesions and between them."

Histologically Pringle's adenoma sebaceum shows a variable picture in different cases as well as in the same patient. The basic change is hyperplasia of not only sebaceous glands but blood-vessels and connective tissue as well. The sebaceous gland hyperplasia is indicated by an increase in number and a more superficial location of the glands plus an increase in number of cells of the basal cell type to several layers instead of the usual single layer. Frequently the latter is the only evidence of hyperplasia. The glands retain their normal structure and the individual cells are normal in size and are not hypertrophied. In addition, the glands attached to hair follicles, their normal location, are also seen, as a rule, to be hyperplastic. The lesion is not encapsulated. Woolhandler and Becker believe the name adenoma sebaceum can be reasonably applied to these lesions in accordance with Ewing's⁸⁷ physiologic rather than strictly morphologic concept of adenoma.

Certain cutaneous lesions occur in asso-

ciation with adenoma sebaceum (Pringle). They consist of small flat fibroma, nevi, papulo-epitheliomus (skin tags), warts, pigmented and depigmented macules, so-called shagreen patch and periungual and subungual lesions (Butterworth and Wilson). Warren and Warvi³²² mentioned that, in accordance with numerous authors, Von Recklinghausen's disease may be suggested by the presence of cutaneous pigmentation, nevi, papillomas and fibromas. In the visceral organs a variety of tumors, fibromas and cysts may be found. Although mental defects, psychoneurotic symptoms and lesions, such as retinal gliomas, tuberous sclerosis and local agenesis of the brain make up part of the syndrome in many cases, in a large number no mental defect is detectable and, in fact, some patients are intellectually above the average. Gunther and Penrose^{113,228} showed that a single dominant gene is probably the main causative factor and in all probability 25 to 50% of all cases are directly due to a mutation in one or another parent.

Treatment of adenoma sebaceum is purely cosmetic. Destructive measures by various means are necessary. Roentgen therapy plays but little part in the treatment.

The variety of findings (widespread congenital abnormalities) which may be found in a patient with Pringle's disease is illustrated by the patient observed at autopsy by Warren and Warvi. The significant findings in this case were: (1) Hyperplasia and hypertrophy of sebaceous glands. (2) Neurofibromata of the skin. (3) Congenital cystic disease of the lungs with pneumothorax on the left. (4) Tuberous sclerosis associated with cystic softening of the left lenticular nucleus. (5) Ovarian leiomyomata. (6) Mesenchymal rests of the kidneys and retroperitoneal tissue. (7) Recent hemorrhages into renal calyces.

Keratotic Adenoma Sebaceum. Among their cases Woolhandler and Becker had one which clinically resembled senile keratosis, but microscopic examination re-

vealed acquired sebaceous adenoma with epidermal hyperkeratosis.

Adenoma of the Sebaceous Glands. Both Warren and Warvi and Woolhandler and Becker admit the possibility of adenoma of the sebaceous glands. The latter authors report a case in which they felt the diagnosis of sebaceous gland adenoma was justified. The former writers state that they consider the term adenoma as appropriate for certain solitary tumors of the sebaceous glands such as were reported by Carol⁵¹ and by others from the Meibomian gland and other locations. The tumors which Warren and Warvi accept as adenoma are rounded non-ulcerated, firm, and consist of a circumscribed overgrowth of sebaceous cells producing masses larger than the usual glands and less regular in shape. These glands frequently lie close to the epidermis rather than in the mid-corium. The lesion suggests an expansile growth of the peripheral portions of the gland. The cells in the center are more normal; those in the periphery stain more deeply, partly as a result of less and more finely divided liposa and partly due to somewhat larger and more hyperchromatic nuclei. Mitotic figures are frequent, numerous or absent. Malignant degeneration of adenomas are frequent. Two of Warren and Warvi's patients with sebaceous carcinoma apparently developed from adenoma.

Nævus Sebaceus. In 1895 Jadassohn¹³³ first described a prenatal type of adenoma sebaceum which is known as nævus sebaceus. He differentiated this from the various types of adenoma and considered it a nevoid growth composed partly or entirely of sebaceous glands of normal structure. This subject was reviewed by Robinson²⁵¹ in 1932 who collected reports of only 35 cases and cited 4 of his own. Savatard,²⁵⁹ Woolhandler and Becker have carefully brought the subject up to date and believe it is produced by prenatal hyperplasia of sebaceous glands, is entirely benign and is of cosmetic interest only. It may occasionally be associated with nævus pigmentosus. According to Sava-

tard this lesion throws no light on the etiology of sebaceous carcinoma. It may be completely eradicated by excision or electrodestruction.

Nævus Pigmentosus et Sebaceus. Adenomatous sebaceous glands may at times be observed in association with other abnormalities which have often been linear nevi. Woolhandler and Becker describe a case illustrative of a combination with pigmented nevi.

Carcinoma of the Sebaceous Glands. The subject of the relationship of carcinoma of sebaceous glands to adenoma and hyperplasia has been fully studied in the excellent paper of Warren and Warvi.³²² They believe that the only carcinoma that can be characterized as sebaceous is one which reproduces in some part the characteristics of the normal gland. They found 29 cases among 4000 cutaneous carcinomas. They include 20 cases of supposed carcinoma of the sebaceous gland not included in Beach and Severance's²¹ review of the literature. There is nothing striking in the gross pathology that would suggest sebaceous carcinoma. The histopathology, however, is distinctive. The cells and pattern of growth closely resemble the normal glands, but even in the most highly differentiated parts there are certain variations from normal structure. The flattened peripheral cells of the normal gland are absent. Instead, the external layer of cells tends to be slightly basophilic and less heavily vacuolated. Most of the tumors in their series were not so well differentiated. In these there is greater variation in size and shape of cells, the nuclei are intensely hyperchromatic, mitotic figures are more numerous, and the lipoid is in finer globules or absent. The cytoplasm may be eosinophilic or basophilic and sometimes keratinized. The typical structure of sebaceous carcinoma may be discernible only in small foci. The tumors grow slowly and ulcerate late. Although the tumors are often resistant to treatment and may metastasize, the prognosis is good if adequate

excision is made early. Even recurrences may be cured by thorough excision.

Tumors of Sweat Glands. Sweat gland tumors are probably fairly common but are rarely seen in the laboratory because they are seldom removed unless they are unusually large. Gates, Warren and Warvi⁹⁷ in their comprehensive review of this subject discuss the following types of change:

- A. Hypertrophy, hyperplasia and metaplasia.
- B. Tumors of true sweat glands.
 1. Syringoma.
 2. Hydradenoma papilliferum.
 3. Hydradenoma.
 4. Hydradenoid carcinoma.
- C. Tumors of specialized sweat glands.
 1. Ciliary gland.
 2. Apocrine gland.
 3. Ceruminous gland.
- D. Tumors ascribed to sweat glands.
 1. So-called sweat gland carcinoma of the breast.
 2. Turban tumors.
 3. Mixed tumors.

Hypertrophy, Hyperplasia and Metaplasia. The sweat gland is not prone to show hypertrophy or hyperplasia as a primary change but may do so as a secondary phenomenon in cases of certain benign neoplasma of the skin. The subject of hyperplasia was discussed by Weidman³²⁴ in 1928. In 1923 Stokes^{278d} presented the case of a girl, aged 19, with lymphangiomatous and hemangiomatous nevus associated with enormous hypertrophy of the sweat glands and localized hyperidrosis on excitement. Epithelial metaplasia, commonly associated with chronic irritation is only occasionally seen in sweat glands. Walther and Montgomery³¹⁵ reported a case of metaplasia of the sweat ducts in the verrucous lesion of the palm of a woman aged 29. The metaplasia, mucinous, did not affect the secreting portion of the glands.

Tumors of True Sweat Glands. The subject of sweat gland tumors is very confused in the literature. Gates, Warren and Warvi⁹⁷ state the essential points of

controversy in differentiation of sweat gland tumors as: (1) distinction from tumors of other structures; (2) differentiation from hyperplasia of the glands; (3) recognition of tumors developing from the secretory and from the ductal portions of the gland. Their discussion of the literature on these points leads to the statement that the subject is still ill-defined, and on the basis of their experience and the literature they recognize four distinctive types of tumors of sweat glands: (1) syringoma; (2) hydradenoma papilliferum; (3) hydradenoma; (4) hydradenoid carcinoma. This terminology is suitable for purposes of our discussion.

Syringoma. This tumor has been designated by a variety of names: Syringoma or syringadenoma (Fiocco, Dohi, Eller, Gans, Unna); syringocystadenoma (McCarthy, Sutton and Sutton, Török); syringocystoma (Neumann, Finnerud and White); hydradénomes eruptif (Jacquet and Darier); épithéliome kystique bénin (Jacquet); cellulome épithélial eruptifs (Quinquaud); cystadenome épithélial bénin (Besnier); lymphangioma tuberosum multiplex (Kaposi); hemangio-endothelioma tuberosum multiplex (Jarisch); spiradenoma (Ewing); nævi cystepitheliomatosi disseminati (Pernet).

Clinically, the lesions affect females, especially at puberty, but may appear first in middle life. They are small, and multiple, but may be occasionally single. The individual lesion is somewhat elevated smooth, colorless, or slightly discolored. The chest and axillæ are especially affected in contrast with epithelioma adenoides cysticum which particularly affects the center of the face. The tumors are radiosensitive. Histologically, they present a typical picture consisting of epithelial groups (dilated cystic sweat ducts) scattered haphazardly throughout the corium without appreciable disorganization of the general architecture of the dermis. The individual unit is a relatively short, narrow, sometimes branching strand of epithelial cells about the diameter of a normal coil duct, which it closely resem-

bles. Cystic expansion, apparently the result of degeneration, adds to the similarity. The absence of myo-epithelium suggests origin from the ducts rather than the coils. The cysts are lined by cuboidal or flattened cells and contain clear fluid or hyaline, or, rarely, horny material. There may be a distinct basement membrane. The sweat glands adjacent to the tumor may be normal, absent or abnormal. Ingels reported a case with histologic features of both syringoma and epithelioma adenoides cysticum. It is commonly believed that the tumor originates from embryonic sweat glands.^{68,242,332}

Weidman and Besançon³²⁵ regarded their case as one of true sweat-gland adenoma, rather than nevus. They could not demonstrate any connection with differentiated sweat glands and raised the question of a possible apocrine gland origin. This concept has been reemphasized by Homma and Escher.¹²² Ormsby and Montgomery²¹⁶ have seen no connection between the apocrine glands and the syringoma. They have seen connections with normal eccrine sweat ducts but not with mature eccrine glands. Gates and her co-workers⁹⁷ observed only 1 case of syringoma in their material.

Hydradenoma Papilliferum. In the general literature of tumors, the name for a papillary growth of variable structure is hydradenoma papilliferum. In the dermatologic literature, however, this type of lesion is known either as *nævus syringadenomatosus papilliferus* (Werther) or as *nævus syringocystadenoma papilliferus*. This usually solitary and slowly growing tumor occurs on the genitalia, perineum, thighs, and face and scalp. The clinical characteristics of the disease are well described by Frieboes,⁹⁴ as follows (cited from Sachs and Lewis²⁵⁷): "The favorite sites are the shoulders, the axillæ, the genitoinguinal and surrounding regions and the hairy portion of the scalp. The lesions are rose-red papules of firm consistency from the size of a millet seed to that of a hemp seed, usually arranged in groups. Owing to their transparent nature, one or

more vesicle-like inclusions may often be distinguished; these inclusions are from the size of a pin-point to that of a pin-head and filled with clear fluid. In addition, the papules are umbilicated at their summit, being similar to lesions of *molluscum contagiosum*. (Because of this finding, solitary lesions of long duration clinically resembling lesions of *molluscum contagiosum* may prove to be nevi of the type under consideration.) The papules stand out discretely or form directly confluent plaques. In 1 case (Kreibich) papillary growths were observed on the surface of such a plaque."

Histologically, the sweat glands are somewhat dilated and the sweat ducts cystic in places. The inner surface of the cavity of the duct contains small, villous-like projections. The lining is composed of two or more layers of cells including an inner columnar and outer cuboidal layer. The epidermis is acanthotic; there may or may not be an associated inflammatory reaction. Stokes^{278a} reported a reaction suggestive of *granuloma pyogenicum*. The nature of this lesion is not definitely known. It has been considered as congenital by some. Other associated cutaneous lesions of an inflammatory nature have suggested a reactive process.

The first case of *nævus syringadenomatosus papilliferus* reported in the United States was that of Stokes.^{278a} Recent publications by Nödl^{211a} and Sachs and Lewis contribute 3 and 5 cases respectively. We have encountered only 1 case among 2500 biopsy specimens of cutaneous lesions examined in our laboratory. Gates, Warren and Warvi review the entire subject and describe under the heading "*Hydradenoma Papilliferum*" the various varieties of lesion which have been reported in the literature as distinctive tumors. These lesions are apparently not all the same.

Hydradenoma. Under this designation, Gates, Warren and Warvi classify a solid tumor of sweat glands. According to them, this is more common than all the other tumors of sweat glands together and less frequently recognized as originat-

ing from these structures. It is a grossly discrete, solitary or multiple growth, sometimes appearing in groups, that is found chiefly, although not exclusively, on the face and scalp. It produces a low, mound-like elevation, except on the scalp where it may be pedunculated. The tumor is frequently located in the subcutaneous tissue and lower corium but may involve the entire corium. Rarely it seems to arise close to the epidermis. Ulceration is unusual. The tumor may be of any size, but is rarely more than 4 cm. in diameter. Growth is slowly progressive to a certain limit and thereafter the lesion usually remains of the same size. Histologically, the majority of tumors consist essentially of alveolar spaces embedded in compactly arranged, solid cell masses and strands.

Sutton^{287a} presented a rare sweat gland tumor composed of discrete nodules unilaterally disposed on the neck of a woman aged 45. Microscopically it revealed cystic and alveolar structures. Sutton explained this lesion, which he called syringocystadenoma nodularis, as a proliferation of sheath cells of the gland rather than as a proliferation of the secretory epithelium. Cooper and McDonald⁶² report a case of adenoma of apocrine sweat glands (hydradenoma) of the anal canals. They believe these tumors are clinically benign (Gates, Warren and Warvi). The nature of hydradenomas is not fully known. They have been considered as arising from hair follicles, and sebaceous glands, as well as from sweat glands and endothelium.

Hydradenoid Carcinoma. Carcinoma of sweat glands has been made the subject of a painstaking research both of the literature and their own material by Gates, Warren and Warvi. A careful study of this portion of their presentation is imperative for anyone desiring acquaintance with this type of carcinoma. Only 6 of their tumors of the sweat gland were frankly malignant. One of them consisted of a lesion around the anus com-

posed of malignant change involving specially the apocrine sweat glands.

Tumors of Specialized Sweat Glands. Tumors of specialized sweat glands, ciliary, apocrine and ceruminous have little clinical importance, and therefore need not be detailed here.

Tumors Ascribed to Sweat Glands. Gates, Warren and Warvi do not recognize the so-called sweat gland carcinoma of the breast as a true tumor of sweat glands but rather as a tumor of mammary epithelium. "Turban" tumors of the scalp, mixed tumors of the skin, seem to be sufficiently unrelated to sweat gland tumors to be discussed separately.

Sheldon²⁶⁶ described 3 cases of sweat gland tumor in which myo-epithelium had undergone neoplastic proliferation, 1 benign, 2 malignant. In 1 case epithelium and myo-epithelium were involved. In 2 cases only the myo-epithelium represented the main tumor element. It is difficult to classify these lesions.

"Turban" Tumors. These lesions, also known as cylindroma, nevo-epithelioma, adenoides, endothelioma capitis, and sarcoma capitis, are characterized by various-sized tumors occurring chiefly on the scalp. There may be similar but smaller tumors on the glabrous skin. The lesions are round, bluish or pink, and firm and usually do not ulcerate. They persist for a long time and are often mistaken for cutaneous metastases. They are more frequent in women than in men. Sachs and Sachs²⁵⁸ reported the first case in a Negro. They are histologically characteristic and have a typical arrangement of basal cells in round, oval, or elongated nests, packed closely so that the tumor is in solid lobules. The neoplastic process in the corium is separated from the epidermis by a narrow band of normal connective tissue. The connective tissue around the tumor masses is degenerated into dense hyalinized sheaths. In certain areas there may be poured-in masses of hyaline in the tumor lobules. The origin of the tumor is questioned. Jones, Alden and Bishop¹³⁶ consider it of sweat gland

origin; Ronchese,^{252a} sebaceous gland; Stilians,²⁷⁷ surface hair follicle; and Binkley,³² of diverse origin. From their exhaustive survey, Gates, Warren and Warvi conclude that the turban tumor is not a special histologic entity and may resemble various slowly-growing epithelial tumors of the skin and its appendages. It has been generally recognized that the clinical and histologic characteristics are those of a benign organoid tumor.

Mixed Tumors of the Skin. These lesions, which occur mostly in the salivary glands, have been the subject of study by numerous surgeons, pathologists and dermatologists.^{1,15,58,77,79,97,116,153,163,181,203,230,249,261,267}

Mixed tumors are a poorly defined group of neoplasms composed of 2 or more types of tissue and characterized by pleomorphism. They are found in all parts of the body and have been attributed histogenetically to each of the 3 germinal layers. Ectodermally derived tumors most often arise in connection with the salivary glands (the majority are situated in the glands or in close proximity to them). Occasionally tumors morphologically identical with mixed tumors of the salivary glands arise in the skin, in the mucous membranes and in glandular structures other than the salivary glands. They are mostly located in the cephalic region, especially in close proximity to embryonic fissures, the lips, the buccal mucosa, the palate and the lachrymal glands. This rare cutaneous tumor is seen on the scalp, and the face, the forearms, the hands, the thighs, the legs. Moorehead claims more have been reported on the trunk. He reports 4 cases of cutaneous mixed tumors located on the skin of the breast, the nose, the sternum and the ear. This is the first instance of such neoplasms arising in the skin of the trunk to have been reported. Histogenesis of the salivary gland mixed tumors and those of the skin and the breast is the same. Among the possible explanations for these tumors are: true teratomata or slowly-growing epithelial

tumors with metaplasia of epithelium and/or stroma.

The pathology of this tumor is especially carefully worked out in the study of Harvey, Dawson and Innes.¹¹⁶ They define the tumors as adenomas of the serous and seromucous glands, salivary or lachrymal, of undifferentiated and gland-lobular types, prone to mucoid, autolytic, self-destructive change of their component tissues. The cells exhibit epidermoid characters both as basal cells and as squamous ones with intercellular bridges and keratinization. On the whole, the tumors consist of polyhedral or spindle-shaped cells arranged in parenchymatous masses, irregular anastomosing strands or islands of closely-packed uniform basophil cells without indication of keratinization. The nuclei are hyperchromatic and the scanty cytoplasm is acidophilic. Mitotic figures are numerous only when the lesion is malignant. The designation mixed is due to the tendency of the epithelium and the stroma to show hyaline and chondroid transformation. Isolation of epithelial cells tends to give them the appearance of cartilage cells within their capsules. Tumors are usually benign and may recur after removal surgically because of incomplete excision. Occasionally malignancy of glandular or epidermal character may ensue. McFarland (1942) aptly stated that "something more than a simple microscopic examination of a section of tissue will be required before an accurate prognosis of a mixed tumor of the salivary glands becomes possible. At present our methods are no more accurate or scientific than the flipping of a coin."

Mucous Gland Tumors in the Skin. Mucous gland tumors studied by Ginsberg and Reuter⁹⁹ are rare. They may occur over any part of the body and even at sites where anatomic considerations would make them unexpected. Ginsberg and Reuter's 2 cases involved the neck and upper part of the chest but the lesions have been found near the ear, in the neck and about the male urethra. Those occurring about the ears, the neck and upper

part of the sternum are usually rests of branchial pouches. Those occurring about the genitalia usually represent disturbance in embryonic development in the closing of the genital groove. Those occurring elsewhere probably arise from sweat glands which undergo metaplasia to correspond to mucous and salivary glands.

Epithelial Cysts. Cutaneous cysts have been classified by Warvi and Gates³²³ as epidermal, traumatic, sebaceous, sweat gland, dermoid and follicular. Excellent reports on the subject of cysts, aside from that by Warvi and Gates, dealing with 566 epithelial cysts, are those of Bishop³⁴ reporting 119 sebaceous cysts; Wein and Caro,³³⁴ traumatic epithelial cysts; Stone and Abbey,²⁷⁹ 363 sebaceous cysts; Dolce and Clark;⁷⁵ New and Ehrich,²⁰⁷ 103 cases of dermoid cysts; Ehrich,⁸⁰ various types of "cutaneous" cysts; Love and Montgomery,¹⁶⁷ on epithelial cysts. Warvi and Gates stated that cysts of the skin may be put into one or another of 3 main groups according to their origin: (a) aberrant squamous epithelium, either congenital or traumatic in origin; (b) overactivity of glands, resulting from general physiologic forces, external conditions, or from some unknown factor; (c) degenerative changes of skin appendages or of benign or malignant epithelial tumors.

The commonest type of epithelial cyst of the skin and all but 10 of Warvi and Gates' 566 cysts fell into this group. They are occasionally the seat of malignant change. Trauma by implantation of epithelium, by altering the structure of cutaneous appendages, or by stimulation of epithelial growth may give rise to cysts. Dolce and Clark report 4 cases of this variety of cysts. Sebaceous cysts may undergo malignant change in as high as 9.2% of cases. Stone and Abbey found 2.2% in their 363 cases, to become malignant. Love and Montgomery, however, do not believe that epithelial or sebaceous cysts should be regarded as precancerous. Hydrocystoma or true cyst of the sweat gland is exceedingly rare. Dermoid cysts are likewise rare. Among New and

Ehrich's 103 cases, there were 4 groups: 49.5% arose from the naso-optic groove; 12.6% about the nose; 23.3% originated from the branchial arches in and about the floor of the mouth; 14.6% were miscellaneous groups of mid-line cysts developing during closure at the mid-ventral or mid-dorsal line. Multiple follicular cysts have been described under a variety of names. We feel that they represent multiple sebaceous cysts [Beerman²⁶]. This type of cyst is well described by Sachs,²⁵⁵ Prakken,²³⁷ and Mount.²⁰⁴

Multiple Benign Cystic Epithelioma (Epithelioma Adenoides Cysticum). These tumors are relatively common. They are usually multiple, with certain clinical and histologic characteristics and those which are primarily tumors of middle age and may be classed with the non-keratinizing tumors. The various names used for this condition are: benign epitheliomata with colloid degeneration; epithelioma adenoides cysticum; multiple benign cystic epithelioma; tricho-epithelioma papillomum multiplex; acanthoma adenoides cysticum; hydradenome eruptif; multiple cystic symmetric nevi; tricho-epithelioma papillomum with syringocystadenoma; cystic basocellular epithelioma; nævus follicularis; Brooke's tumor; adenoid cystic epithelioma. Excellent reviews on the subject are those of Summerill and Hutton,²⁸³ Savatard,^{259b} Ingels;¹³² Goldman,¹⁰³ Traenkle,³⁰⁴ Nisbet,²¹⁰ and Warvi and Gates.³²³ This dermatosis begins usually at the age of puberty and is usually hereditary (Goldman) and occurs mostly about the face. It was originally described by Brooke⁴⁰ and by Fordyce.⁸⁸ They believed that these lesions sprang either from the basal layer of the epidermis or from similar cells in the hair follicles. Traenkle showed that most multiple benign cystic epitheliomas are histologically tricho-epitheliomas and may show great variation in degree of differentiation in respect to hair follicle structure. The more mature forms of the latter structures could be more properly designated hamartoma than epithelioma. Malignancy has

been described following irritation or improper treatment. Warvi and Gates reserve the term epithelioma adenoides cysticum for a benign lesion of hair follicles which is grossly indistinguishable from syringoma and, like it, multiple and familial. The so-called syringomatous type, they believe, is properly classified with the tumors of sweat glands.

Cutaneous Cancer and Precancer. We shall not attempt to detail the numerous studies on the nature and cause of malignancy. Mention of some of them, however, is pertinent to the understanding of the problem of cutaneous involvement. The skin has not been found adaptable to *in vitro* tissue culture studies, both because of difficulties of handling and measurement and also because normal epidermis cannot be carried in tissue culture over long periods without developing cornified layers which eventually cut off the living elements from the surrounding medium (Pinkus,^{232a} Cholpin⁶⁵). Höfer¹²⁰ has shown *in vitro* that both malignant and normal epithelium of the cornifying type behave alike, so that, as Pinkus^{232a} thinks, there is little possibility of keeping these tumors alive and growing for any considerable time (Coman^{59a}). Coman has, however, contributed a convincing piece of evidence that there is decreased cohesiveness in cells from squamous cell carcinomas of lip and cervix as compared with normal squamous epithelium or that from a benign tumor. This was measured in milligrams by a method dependent upon the bend produced in a microneedle when a pair of cells was pulled apart. He suggested that this property of the carcinoma cells may be related to a lowered calcium content of these cells.^{59b} This lack of cohesiveness of cancer cells had been inferred by Cowdry,⁶⁴ who stated that "perhaps decrease in stickiness of carcinomatous cells is a necessary prelude to their invasiveness." Amersbach and his associates,^{9,10} utilizing skin respiration as a dermatologic tool, tested the concept of Warburg²¹⁶ that an altered kind of internal respiration is characteristic of and, in fact, is the

cause of tumors. Their study of a number of precancerous and cancerous lesions of the human epithelium and of the normal epithelium from the same general area showed that in the majority of cases there was a tendency to depression of the O₂-CO₂ respiration of the precancerous and cancerous lesions. This phenomenon, if it could be placed on quantitative basis, might be another method for predicting the really "precancerous" nature of a lesion.

The nature of cancer's origin is a subject of profound debate. Sutton, Jr.,^{285a,b} has presented his views on the manner of growth of epithelioma of the skin in two scholarly papers. His thesis is that cancer is a cellular disease. It begins probably in one cell, the progeny of which form a colony of cells, which is the cancer. A solitary cell may possess all the attributes of the cancer state within itself. Histologic evidence shows that carcinoma of the skin in its earliest stages appears to originate in one cell. Neoplastic lesions of the epidermis may be classified in accordance with a slow or swift growth of the altered cells and their strong cohesion, weak cohesion or lack of cohesion. All neoplasms of the skin in which the cells resemble those of the Malpighian layer in undergoing keratinization form a single set, the clinical subdivisions of which are determined by the degree of cohesion and rate of growth. This theory does away completely with the concept of "precancerosis." Small lesions are neoplastic or not. If neoplastic, they may grow slowly and be benign, or grow fast and be malignant. Sutton subscribes to the theory of the origin of cancer in somatic mutation. This theory postulates that genetic alteration of somatic cell may result in the production of a colony which is cancer. The new cells differ from normal ones mainly in the rate of proliferation and capacity for organization. Neoplasms produced by filterable agents are not satisfactorily explained by this theory. His observations consonant with this theory show how epidermal carcinoma begins from few cells

(probably only one cell) and progresses with no fundamental change excepting continued proliferation. In his study of the manner of growth of cutaneous epithelioma, Sutton, Jr., reaffirmed his belief that the evidence presented supports the view that clinically and histologically each spontaneous epithelioma of the human skin behaves like a colony of cells of a new kind and perhaps the new kind comprises the homogeneous progeny of one mutant cell. Montgomery¹⁹³⁰ takes exception to Sutton's classifying epidermal neoplasms on the basis of cohesion of the cells rather than by the widely accepted method of classification and grading of Broders. He does agree with Sutton that the benign or malignant change that may develop in the future cannot be predicted accurately either clinically or pathologically. He also denies that the theory of mutation in the origin of cancer does not preclude the concept of precancerosis but simply tends to explain epithelioma *in situ*. Sutton's (1942) reply to Montgomery leaves the proposition still one susceptible of much polemic debate and little hope for immediate settlement.

As indicated above, the skin is unique (excepting the eye) in its accessibility for study; but it also is so situated as to be influenced by numerous environmental factors from which other organs may to some extent be exempt. Hueper^{129b} and Warren³¹⁷ have contributed extensively to our knowledge of cancer in its relation to occupational trauma and environment. Environmental cancer is one due to prolonged contact with some cancerigenic agent in the environment. The relationship of a previous exposure to such an agent and the cancer often appearing many years later is frequently overlooked or not understood. Environmental cancers can be divided into 4 main groups according to the type of exposure: (1) cancers caused by agents in the normal environment (due to the continued ingestion of arsenic in drinking water and food-stuffs in certain regions, the solar cancers, etc.); (2) cancer resulting from certain

habits (habitual cancer), as for example cancer of lip and mouth in smokers, cancer of the oral lining in betel and tobacco chewers, and cancer of the abdominal skin in kangri users; (3) cancer resulting from use of certain medicinal agents (medicinal cancers), *e. g.*, cancer of the skin after arsenical medication and after exposure to Roentgen rays and radioactive substances; (4) occupational cancer elicited by exposure to chemical and physical agents in the course of regular occupations (most important group).

The chemical and physical agents known to cause cancer (or suspected of causing it) are arsenic, chromates, nickel carbonyl, radium, mesothorium, asbestos, crude and processed mineral oils, pitch, tar, soot, paraffin oil, anthracene oil, creosote, aromatic amino compounds (aniline, naphthylamine, benzidine), benzene, ultraviolet rays, Roentgen rays, radioactive materials and substances from certain parasitic worms. A review of recent advances in cancer research by Lewisohn¹⁵⁸ gives a detailed discussion of carcinogenic substances. We shall refer to those which specifically are of great importance to cutaneous oncology. For general, and easily available recent discussions of the biology and pathogenesis of cancer, the reader is referred to the reports of Cramer⁶⁵ and of Spencer.²⁷¹ Brief notes on colchicine as a growth stimulator²⁰⁸ and on the genetic aspect of the enzyme-virus theory of cancer²³⁶ have recently appeared.

Just as the skin because of its location is exposed to various insults, it is an organ demonstrated to have great immunologic powers. Even in the case of cancer, it has been proposed that the production of curable cutaneous carcinoma by irritations which are not carcinogenic to internal organs may save some lives by preventing cancer of the internal organs. For example, Peller and Stephenson,²²⁷ from observations on United States Navy personnel, assumed that cancer of the lip and skin exerts a beneficial (*i. e.*, inhibiting) effect on developing cancer elsewhere. Peller²²⁶ had claimed from occupational mor-

tality statistics of England and Wales (1921-23) that an increase of carcinogenic irritation leads to an increase of cancer in more inaccessible organs. Furthermore, Eisenstaedt⁸¹ noted that although superficial epitheliomas exhibited marked tendencies toward multiple cutaneous neoplasia, they do not show tendencies toward multiple malignant tumors elsewhere in the body. The studies of Conrad and Hill⁶¹ and of Shields Warren and Gates,^{318a} on the other hand, showed no inverse relationship between mortality from cancer of the skin and lip and mortality from cancer in other sites. On the contrary, Warren and Gates,^{318b} in a more recent work involving 1149 carefully studied cases of cancer of the skin, and confirmed by the series of Lombard and Warren,¹⁶⁴ found that there was no justification for recommending the induction of cancer of the skin to protect against the development of cancer elsewhere. In the group with cutaneous cancer there was definitely more cancer of organs exclusive of the skin than would be encountered in a similar population drawn from Massachusetts at large. Cancer of the skin does not protect against the development of cancer elsewhere. As with other types of cancer, cancer of the skin is associated with a greater number of multiple cancers than would be expected on the basis of chance. These new findings sound a note of warning that those dealing with cutaneous malignancy should look for other foci of carcinoma in the body. They also re-emphasize the unjustifiable complacent attitude and satisfaction of dermatologists with the superficial significance of cutaneous cancer.

If trauma is a cause of carcinoma, the skin, because of its exposed position, would be especially predisposed. In spite of this, there is no clear-cut evidence definitely to associate trauma and cutaneous carcinoma. Lutz¹⁷⁰ thought that acute trauma could lead to carcinoma (1) in old persons in whom injury in atrophic skin may lead to cancer, (2) in persons burned with hot tar, (3) in those with skin injury

and prolonged presence of a foreign body, and (4) young persons whose skin shows no visible degenerative changes. The effect of environment and occupation in the induction of carcinoma has been touched on elsewhere in this review. Shields Warren³¹⁷ defined the minimal criteria required to prove causation of traumatic or occupational neoplasms. He accepted a tumor as due to mechanical trauma under the following circumstances: (1) integrity of tumor site prior to injury must be established; (2) the injury must be sufficiently severe to disrupt the continuity of the tissue at the site; (3) the tumor must follow the injury by a reasonable time; (4) the tumor must be of a type which might reasonably develop as a result of the regeneration and repair of those tissues which had received the injury. These criteria seem to us a reasonable set of requirements for critical evaluation of a case purporting to be traumatic in origin. Warren believes that single trauma rarely if ever causes cancer. An interesting example of mixed epithelioma of the back arising from daily application of a phenol and ergot ointment, reported by Stevens and Callaway,²⁷⁵ may be cited as a reminder of the possibility of traumatic (irritation) cancer from seemingly harmless sources.

The exposed situation of the skin permits of early diagnosis and cure of carcinoma, but contrary to expectation much procrastination by physicians and the laity leads to late cutaneous malignancy with its irreparable if not fatal consequences. This fact is all the more surprising because it is possible, in a high proportion of cases, for a competent clinician not only to diagnose the presence of carcinoma of the skin but actually to indicate the histologic type of tumor. It is true that if treatment is adequate, the histologic verification of the diagnosis is not needed to produce favorable results. Warren, Simmons and Rea³²¹ studied 829 treated carcinomas of the skin not verified by biopsy. Of these cases, 84% were followed for 5 years. There were 57%

3 year and 48% 5 year cures of all the tumors treated. If the cases lost and dead of intercurrent diseases are counted as cures, the 5 year cures would rise to 84%. If they are entirely excluded, the figures would be 76%. Recurrences occurred in 13% of cases showing primary healing followed 1 year or more. Primary healing occurred in nearly all cases (98%). More than 25% of the deaths from cutaneous carcinoma occurred after primary healing, so that primary healing cannot be taken as a criterion of cure. These authors regarded failures as due to the use of lightly filtered radon applied to the surface in inadequate dosage and feel that Roentgen rays or radium used at a distance might have given better results. They do not feel, in spite of these good results, that the *lack of biopsy alone* was responsible for a better showing in this group than in one previously reported by this group for a biopsy verified series of cases. It is not difficult to understand the good results in Warren, Simmons and Rea's study when one realizes that these authors may unconsciously have made accurate diagnosis clinically in a high proportion of their cases and instituted therapy accordingly. That a high degree of accuracy in diagnosis may be attained by competent observers (not casual observation by the average practitioner) is indicated by the well-controlled study of Torrey and Levin,³⁰¹ who noted that the clinical diagnosis of epithelioma was found to be correct for 90% of the lesions, the clinical differentiation between basal and squamous cell epitheliomas was correct for approximately 75%, and 15% clinically diagnosed as benign were found to be epitheliomas. In spite of this apparently easy clinical differentiation, we agree with Warren and his associates³¹⁹ that biopsy of all skin tumors is essential for the establishment of rational treatment of skin carcinomas. It also appears to us, however, that a certain amount of classification of the forms of differentiation of basal cell carcinoma serves some

useful clinical purpose in regard to prognosis.

Schrek and his co-workers^{262a,b,c,d,263} of Huntington Memorial Hospital of Boston and of the Pondville Hospital, Wrentham, Mass., and the Hines Hospital, Hines, Ill., have furnished the literature with comprehensive data on cutaneous carcinoma. This series of articles gives a detailed analysis of: (1) the similarities and differences between basal cell and epidermoid carcinoma; (2) the characteristics of value in differential diagnosis; (3) the efficacy of treatment; (4) the value of grading; (5) the racial distribution of cancer.

Among 581 cases of cutaneous carcinoma the median duration of basal cell carcinoma (3.5 years) was much greater than that of epidermoid carcinoma (1.2 years). The median sizes of the two types of tumor were, however, the same (1.9 cm.). Size, not duration, of the tumor prompted the average patient to seek hospital treatment. At the time of hospitalization the median age of patients was 64.2 years for those with basal cell lesions and 68.2 years for those with epidermoid carcinoma. The median age at time of onset was 57.3 years, and 66.2 years for basal and epidermoid carcinomas respectively. Basal cell lesions develop, therefore, in younger persons than do prickle cell lesions. The findings as to median durations and median ages at time of hospitalization and at time of onset were confirmed by a series of 495 cases of cutaneous carcinoma at the Pondville Hospital. The patients were on an average somewhat older than those of the Huntington Memorial Hospital.

Innate malignancy (the degree of deviation of the tumor from the prototype) of basal cell and epidermoid carcinoma as measured by the median growth rate and the percentage of tumors metastasizing and clinical malignancy (hazard of the tumor to the life and health of the patient) indicate that epidermoid carcinoma is about 3 times as malignant as basal cell carcinoma. But in spite of its low malig-

nancy basal cell type recurs in as high a percentage of cases as the epidermoid type.

The degree of innate malignancy of cutaneous carcinoma may be measured by: (1) the amount of anaplasia of the tumor cells; (2) the growth capacity of the tumor; and (3) the capacity of the tumor for metastasis. Broders³⁹ classification is rated as of theoretical interest and clinical importance by Schrek but of limited scope of application, since its usefulness is confined to comparison of tumors arising from a common prototype. It is common experience of pathologists to have the same tumor graded variously by different observers and indeed for the same block to show various grades of activity. Broders, however, regards his method of grading as of value in treatment and prognoses. Casey⁵² measured malignancy by means of the mitotic index which Schrek considers an indirect method of determining the growth capacity of a tumor. Schrek advises the use of the growth rate as a measure of growth capacity. This can be applied in the comparison of tumors arising from different prototypes as to innate malignancy: Wilson³³⁶ studied 3221 cases of epithelioma of the lip and skin to correlate the rate of ulceration with such factors as grade of malignancy of the lesion, type of treatment and age of the patient. Of these cases, 793 had been previously used by Broders as a partial basis for grading of cancer and 268 cases of basal cell cancer had been reported by him. In cases of squamous cell epithelioma, the rate of ulceration was found to be directly proportional to the grade of malignancy except with lesions of Grade 4, which were found to ulcerate at a rate between those of Grade 1 and Grade 2. Previously treated epitheliomas were found to ulcerate more rapidly than those which had not been treated. In recurrent epitheliomas, the rate of ulceration was found to be most rapid in the growths previously treated with pastes and salves. Ulceration was more rapid in persons over 56 years of age than in younger individuals. The question of metastasis as an index of

malignancy is affected by other factors than innate malignancy. These include character of the blood supply, the lymph drainage, site of tumor and trauma. MacCormack,¹⁷¹ for example, found that among 108 cutaneous carcinomas, 31 extended to the lymph nodes. This was less than is the case for lesions of the mucous surfaces. Schrek^{262a} indicates that the malignancy of a tumor from the clinician's viewpoint is likewise affected by a number of factors. The chief of these is innate malignancy, but location and type of therapeutic intervention are of paramount importance. Clinical malignancy is measured, as a rule, by the percentage of 5 year cures, by duration of life in treated and untreated patients, by survival curves, by life expectancy curves, percentage of patients with recurrences and percentage of patients dying with the malignant growth.

Epidermoid carcinoma has a tendency to be distributed to the ears, the hands and the lower part of the face, in order of frequency. Basal cell carcinoma prefers the upper part of the face, the nose and the ears. Both types occur more frequently in males than in females. This is especially true for tumors of the ears. Tumors of the scalp, trunk and legs were more frequent in the female. Of Schrek's tumors of the scalp, trunk, arms and legs, 18% developed in preëxisting scars which were produced by such injuries as burns, lacerations, surgical operations and ulcerations. If scarred skin is more susceptible to carcinoma, it is evidence of the possibility that a single traumatic injury may eventuate in carcinoma. About 16% of epidermoid carcinomas metastasized to the regional lymph nodes. This was not appreciably conditioned by the site of the tumor.

Cutaneous epitheliomatosis is much less frequent in Negroes than in the whites. In the Tumor Clinic of Edward Hines, Jr., Hospital, Schrek^{262d} found among 10,857 white and 724 colored male patients with cancer that cutaneous cancer occurred in 19.2% of the white patients and in 2.8%

of the colored group (7:1). Carcinoma of the exposed skin is much less frequent in colored than in white persons, but carcinoma of the covered skin has the same incidence in the two races. In the white race cutaneous cancer is more prevalent in the southern than in the northern states. White men have a higher incidence of cutaneous cancer than white women, but no sex difference was noted in the colored race. A high percentage of cutaneous carcinoma in colored patients developed in a preëxisting scar (none followed a war injury) or in a chronic inflammatory lesion. A low percentage of scars gave rise to an epithelioma. In his study Schrek surveyed the racial distribution of cancer, based on the records of the Hines Memorial Hospital, of the U. S. Public Health Service on the prevalence of cancer, and on the mortality statistics of the United States. Carcinoma of the exposed skin and of the lip, and keratosis of the skin had a very low percentage in the colored. Carcinoma of the covered skin, however, as previously stated, had approximately the same percentage in the colored as in whites. Exposure to sunlight and other climatic conditions is considered the major etiologic factor in carcinoma of the exposed skin in the white race. Scars and chronic inflammatory lesions are, apparently, important etiologic factors in carcinoma of the exposed and covered skin of Negroes and also in carcinoma of the covered skin of the white race. No analysis of the relation incidence of syphilis in the two groups and its relation to cutaneous cancer in the two races was included in this study.

Sunlight and Cancer of the Skin. This subject has been fully reviewed up to 1942 by Beerman and Stokes.²⁷ Since this summary was made, light as a factor in skin cancer has been emphasized among others by Weiss and Conrad,³³¹ Hueper,^{129a} and Hueper and Figge.¹³⁰ Hueper demonstrated that the epidermis of the rat is capable of producing under proper stimulation (ultraviolet rays, arsenic) as great a variety of carcinomas as that seen in the

human skin. With Figge he produced circumstantial evidence in support of the hypothesis that porphyrin metabolism associated with the excretion of relatively large amounts of porphyrin by the Harderian glands is one of the factors that influence susceptibility to light induced cancer in rats. The rôle of sunlight as a factor in the production of cancer is mentioned above in the section dealing with the generalities of the cancer problem.

Pseudo-epitheliomatous Hyperplasia. Pseudo-epitheliomatous hyperplasia in chronic inflammation has long been difficult to differentiate from cancer of the skin. White and Weidman³³³ emphasized the extent to which it develops histologically at the margins of ulcers. Every gradation up to perfect imitation of epithelioma may occur so that it becomes impossible to distinguish histologically between squamous cell epithelioma and non-malignant hyperplasia. These authors believe that a diagnosis of carcinoma is not justified unless the infiltration extends to the level of the sweat glands or farther, or when the pathologist has had wide acquaintance with the behavior of hyperplastic epidermis in general. Winer³³⁷ in his review of this subject has summarized the diagnostic characters which have been reported to differentiate hyperplasia from true cutaneous carcinoma. He concluded that the most frequently noticed histologic finding was the edema of the upper part of the cutis and in the epidermis of all the sections which showed pseudo-epitheliomatous hyperplasia. The edema caused vacuolization of the intercellular spaces in the lower epidermis and disintegration and vacuolation of the epidermal cells in the upper epidermis. Although the edema was diffuse, the pseudo-epitheliomatous proliferation was, as a rule, localized to a single area. Therefore, the factor of nutrition must be considered as being a possible cause of the hyperplasia. This epithelial change has been noted in a number of cutaneous diseases among which are: granulomas; tuberculosis (scrofuloderma and lupus vulgaris);^{144,190,309} syph-

ilis;^{150,302,333,337} deep ringworm (blastomycosis; sporotrichosis; actinomycosis);^{121,196,333,337} iododerma¹⁹⁶ and bromoderma;¹⁰¹ ulcers,^{333,337} traumatic ulcers,¹⁵⁵ verrucous lesions;¹⁰⁵ molluscum contagiosum;³²⁴ multiple pyoderma.¹⁸⁵

Diagnosis of pseudo-epitheliomatous hyperplasia may be facilitated by identification of histologic features of the associated dermatosis. For example, in syphilis and tuberculosis the characteristic changes in the cutis are helpful in ruling out epithelioma. The deep fungus infections have fairly characteristic histologic pictures. For example, blastomycosis is identified by epidermal abscesses and the causative organisms. Verrucae and condylomas may offer real difficulty. The hyperkeratosis and parakeratosis, the extreme regularity of the acanthotic process and the intact basement membrane are the differential points. Winer emphasizes that a spontaneous healing in "epithelioma" means pseudo-epitheliomatous hyperplasia.

Precancerous Dermatoses. This term is used loosely by dermatologists to include dermatoses with an incidence of epithelioma no greater than should be expected if certain environmental and other factors, all of which predispose to cancer, are considered, *viz.*, age, senile changes, light sensitivity, chronic irritation, trauma, etc.²¹⁶ Some believe the name should be confined to true but rarely encountered cases of Bowen's disease, senile keratosis, arsenical, tar and Roentgen ray or sunlight keratosis and to leukoplakia. Various other diseases, including syphilis, are not classed as precancerous. The so-called precancerous condition is not necessarily represented by an epithelial hyperplasia; in fact there may be epithelial atrophy as in radiation dermatitis, xeroderma pigmentosum and kraurosis vulvæ. The precancerous concept has been criticized by many, since, although there is no clinical malignancy, there is already the histologic picture of squamous epithelioma *in situ*.^{82,172b,188,216,286b}

Arsenical Keratosis and Carcinoma. Arsenic is apparently an ubiquitous sub-

stance and its widespread use yields countless possibilities for its introduction in the body. The latent interval of many years between administration of arsenic for medicinal purposes and the onset of adverse cutaneous and other organic processes leads to much misunderstanding and to a number of clinical entities which only a thorough knowledge of the effects of arsenic on the skin and other organs will clarify. That this unawareness of the effects of arsenic on the skin in the production of keratoses and cancer is not generally known is evidenced by the numerous times in various tumor conferences that the Reviewer has surprised the assembled specialists by "digging out" a history of arsenic ingestion in what to a dermatologist is an obvious case of arsenical hyperpigmentation and keratoses. Although much literature has accumulated on the arsenic problem, the *modus operandi* of this agent in carcinogenesis is still a mystery. Excellent recent reviews on the general problem and its oncologic aspects are available.^{20,36,49,90,193c,201,250}

The lesions of arsenic in the skin are distinctive. The palms and soles especially are affected by clavus-like elevations of varying size (2 to 5 mm.) and elevation. They may be picked out of their keratotic beds. Superficial ulcers or fissures may occur where these horny lesions have been traumatized and carcinomas may develop either in the fissures, the ulcerated or hyperkeratotic lesions themselves. Over the rest of the body, flat, discrete, reddish, sharply delimited, scaling keratoses may occur 0.5 to 10 mm. in diameter with raised pearly borders. Sometimes these lesions undergo malignant change. New lesions resemble psoriatic patches and may, in fact, arise in psoriasis for which the arsenic was given. These keratotic lesions are unlike ordinary senile keratoses in that they are not entirely on the exposed surfaces of the body. They are often associated with varying degrees of hyperpigmentation of the skin resembling "raindrops on a dusty road."

In addition to the cutaneous changes,

some of the patients may show other effects of the arsenical. We have seen, for example, neuritis, hepatitis, with and without ascites, pulmonary metastatic carcinoma, and Franseen and Taylor noted patients with carcinoma of the esophagus, and carcinoma of the pancreas. Neither of these latter lesions were at the sites of excretion and they gave little evidence for the occurrence of arsenic induced carcinoma of the internal organs. Other authors have also found little evidence for internal organ carcinoma of arsenical origin in patients who had received arsenic.

The type of arsenic which produces these late cutaneous changes is usually pentavalent. This was shown by the work of Osborne and his colleagues,^{217,218} extending the work of Brünnauer,⁴¹ using a method to precipitate arsenic as trisulfide crystals in tissue sections prepared from arsenical keratoses. He found that the largest arsenic deposits were in the papillae of the corium and in the basal layer of the epidermis. The coil ducts and glands contained large quantities of arsenic, and considerable amounts were found in the hair follicles. Osborne's group suggested that the mechanism of production of arsenical keratoses seemed to be the speeding up of the keratinization cycle by the deposit of an irritant in the form of arsenic in the upper corium, papillae and epidermis, and the stimulation of the basal layer in the same manner could probably explain the carcinomas. Trivalent arsenic, on the other hand, had more effect on the vascular elements of the skin and produced a different picture. Unfortunately there is not complete agreement in the literature regarding the reliability of Osborne's method. Tannenholz and Muir²⁹² believe they had demonstrated similar crystals in controls as in the experimental material. Although in 1941 Becker^{23c} as well as Oppenheim²¹⁵ cited others in confirmation of Tannenholz and Muir's conclusions, Montgomery and Waisman felt that Osborne's method was valid. Further evidence suggestive of the correct-

ness of the arsenical findings in lesions is the demonstration in hair and nails (especially the slow-growing pubic hair) or arsenic many years after its administration.¹¹⁷ The mechanism of action of arsenic as a carcinogenic substance is unknown. Montgomery and Waisman believe it can stimulate latent or dormant foci of epithelioma.

Montgomery^{193c} found that in 20% or more of the cases of keratosis from arsenic, epithelioma develops, again starting out as squamous cell epithelioma *in situ* with various phenomena of keratinization of individual cells. The histologic changes duplicate those in cases of Bowen's disease and senile keratosis. In addition, there may be a peculiar type of vacuolization of the cells of the epidermis. Anderson^{11a} maintained that Bowen's disease and superficial epitheliomatosis are predominantly the result of the ingestion of arsenic.

Milch¹⁸⁹ stated that squamous cell epithelioma with typical pearl formation has invariably been reported by observers of this condition. Franseen and Taylor did not distinguish between superficial epitheliomatosis and superficial epithelioma developing after the ingestion of arsenic and he then reported many cases of basal cell epithelioma which Montgomery^{193b} says were erroneously attributed to arsenical medication. Anderson and Franseen and Taylor made no arsenical determinations in their cases. In a later study Montgomery and Waisman²⁰¹ state that by proper evaluation of various findings the distinction between epithelioma provoked by arsenic and the lesions of superficial epitheliomatosis and Bowen's disease can be made. In this study the authors believe they have confirmed the concept that arsenical epithelioma is associated with a local concentration of arsenic in the tissues. In contrast with this, the superficial epitheliomatosis usually shows no storage of arsenic. They state that epithelioma provoked by arsenic usually is relatively benign. Our own

experience suggests that this viewpoint is too optimistic.

Treatment of the epitheliomatous lesions due to arsenic should be radical, surgical or electrodestruction. Radiotherapy is inadequate. Developing lesions should be looked for and treated.

Bowen's Disease. In 1912 Bowen presented 2 cases of chronic atypical epithelial proliferation in which there was a solitary lesion composed of lenticular papules which resembled nodulo-ulcerative cutaneous syphilis. He named it "precancerous dermatosis."³⁷ An early lesion is usually a firm, pale red papule covered with a thickened horny layer and cornified crust. Beneath the crust, the surface might be red and oozing, granular or slightly papillomatous. The plaques may be annular or serpiginous in outline and may extend peripherally and heal in the center. Many of the cases develop squamous cell epithelioma with metastasis and death. It is claimed by some (carefully reviewed by Cipollaro and Foster⁵⁶) that Bowen's disease may occur on the mucous membranes (cornea, Wise³⁹). Montgomery,¹⁹³⁰ on the other hand, believes that the term "Bowen's disease" has been used loosely in the literature and that many cases reported as occurring on the mucous membranes are simply cases of squamous cell epithelioma with phenomena of individual cell keratinization. He believes the term should be limited to those lesions resembling Bowen's original description, simulating nodulo-ulcerative syphiloderm, and possibly to the type of multiple lenticular plaques described by Darier and by Fraser.⁹¹ Montgomery had opportunity to study a total of 10 cases of this disease. In all but 1 of them there was a solitary plaque and in all of them the disease was limited to the glabrous skin. These lesions had existed for from 6 to 30 years without history of any kind of progression in the size of the lesions. Contrary to the findings of Anderson,^{11a} Cipollaro and Foster,⁵⁶ and Arguello, Ferraris and Tello,¹² Montgomery could find no history of arsenic inges-

tion nor evidence of arsenical pigmentation keratosis or superficial epitheliomatosis. Arguello and his co-workers' case seems to the Reviewer like an ordinary arsenical keratosis with epithelioma.

The histology of Bowen's disease is not diagnostic but is, according to Montgomery (1939), common to all true precancerous dermatoses. He summarized it as being that of a squamous cell epithelioma *in situ* with the phenomenon of individual cell keratinization. Others, however, think the picture is characteristic. Briefly the changes are stated by Anderson (1932) as consisting of hyperkeratosis and acanthosis. The acanthotic epidermis presents large cells with deformed nuclei, multinucleated cells, numerous mitoses, disordered polarity, irregularity in the size and shape of the cells, irregularity of the staining qualities of the nuclei, together with large cells having a vacuolated cytoplasm with granules of chromatin. The corium contains a certain amount of reactive inflammation. Civatte (cited by Marques¹⁷⁷) depicted 2 histologic types of Bowen's disease one of which becomes in basal cell epithelioma, as reported by various authors (Grütz,¹¹¹ Gutman,¹¹⁴ Goldberg,¹⁰² Szodoray²⁹¹). This is denied by Montgomery. It is, from the beginning, histologically a squamous cell epithelioma.

Many cases of Bowen's disease show penetration of the basal cell layer of the epidermis with resultant invasive squamous (prickle) cell carcinoma. Stout^{280d} cites a case to illustrate the possibility of metastasis from Bowen's disease without discovery of gross or microscopic evidence of penetration of the basement membrane.

The cause and origin of Bowen's disease is unknown. It has been considered variously as arising from the sebaceous (Rousset²⁵⁴) or sweat glands (Grzybowski,¹¹² Jorno¹³⁷) or as a delayed nevus (Grütz¹¹¹). The arsenical factor in its etiology has been mentioned above.

The treatment of choice is superficial excision. Radiotherapy is not advised because of the similarity of the histologic

findings to that of early Roentgen ray or radium epithelioma.

Erythroplasia of Queyrat. This "precancerosis" was first described in the American literature by Sulzberger and Satenstein.²⁸² It had originally been presented by Fournier and Darier⁸⁹ in 1893 as *épithéliome papillaire nu*. Queyrat²⁴¹ in 1911 designated the process, after much study, as *erythroplasie*. Since then it has been variously known as the *erythroplasie* (erythroplasia), *erythroplakie* (erythroplakia) of Queyrat, or psoriasiform carcinoma of the glans penis.^{259c} Numerous cases have been described in the *Archives of Dermatology and Syphilology* since Sulzberger and Satenstein's report. This process so uniformly becomes cancerous and is so prone to metastasis that Sulzberger and Satenstein regard it as a true precancerosis. It occurs chiefly on the penis (glans), glans clitoris, and other parts of the vulva, the lips, the buccal mucosa and rarely the skin itself. Syphilis frequently is found associated with it but it is definitely not the cause. As noted elsewhere, Montgomery regards erythroplasia as a variant of leukoplakia; and states that histologically it is epithelioma *in situ*.

Darier's description of this lesion is quoted from Sulzberger and Satenstein as follows:

Erythroplasia is found on the buccal mucosa, the tongue, the lips, the cheeks, the glans penis and the foreskin, or on the vulva in the form of a well-circumscribed, erythematous surface, which is velvety and shiny. Its etiology is unknown. Syphilis is not regularly present in these patients. This condition grows very slowly, persists indefinitely and resists all topical remedies; excision or total destruction by cauterization or, preferably, with carbon dioxide snow is necessary, for sooner or later an infiltrating prickle cell epithelioma develops, with early involvement of the regional glands. The differential diagnosis must consider a syphilid, a lupus vulgaris of the mucous membrane, a basal cell epithelioma and, on the genitals, a diabetid (Monilia). In the cases which I know, histologic examination has shown slightly variable lesions. Those which

seem to me to be the most characteristic consist of hypertrophy of the rete pegs, without dyskeratosis; these, increased in length and in breadth, are superficially abraded; one finds a moderate cellular infiltration in the upper parts of the cutis. In other cases, clinically identical, one has found dyskeratotic changes which are definitely of the type of Bowen's disease (Hudelo and Cailiau, Richon, on the vulva; G. Barbier, on the mouth), (Sulzberger).

Because of the early malignant changes with metastasis, treatment should be radical destruction.

Extramammary Paget's Disease. Paget's disease of the nipple is a relatively well-defined entity both clinically and pathologically and in the last analysis since the majority of the cases (75% Montgomery^{193f}) are associated with an underlying carcinoma of the breast, this disease should be considered apart from the cutaneous manifestations as a disease of the breast. Extramammary Paget's disease of the skin has been claimed to be a variant of Bowen's disease, or to represent superficial moist squamous cell epithelioma or metastatic carcinoma (Montgomery, 1937) or as due to the intra-epidermal spread (a) of carcinoma of the apocrine glands (and perhaps of other cutaneous glands), (b) of carcinoma of mucous membranes bordering on skin, and (c) possibly of melanoblastoma (Pinkus and Gould²³³).

In their review of this subject, Parsons and Lohlein²²⁴ state that extramammary Paget's disease has rarely been reported. Weiner³²⁸ in his compilation was able to collect reports of 57 such cases and reported 1 additional case. He finally decided on 15 (including his own) as being true instances of this rare disorder. In 4 of these, the disease involved the male genitalia, in 8 the vulva and in 3 the axilla. Pinkus and Gould, not accepting all of Weiner's cases, reduced the total to 9. Among these 9 there were cases rejected by Weiner and accordingly Parsons and Lohlein are inclined to accept Weiner's 15 cases as the more nearly correct figure. At any rate the number of cases is exceedingly small.

According to Parsons and Lohlein, the term "extramammary Paget's disease" should be restricted to those cases in which the lesion occurs apart from the breast and its covering skin, and is from the standpoint of histology entirely similar to the classic lesion in the breast (*i. e.*, epidermal changes essentially identical with those observed in Paget's disease of the nipple and areola) and in addition carcinoma of the underlying sweat glands. This is essentially the definition of Stout.²⁸⁰

Leukoplakia. Leukoplakia is characterized by grayish white plaques on the oral and genital mucous membranes. The sites of predilection for this dermatosis are: buccal mucosal interdental line (made by teeth of upper and lower jaw), the gums above the upper canine teeth and lateral incisors; the sulcus beside the upper and lower gums in the roof and floor of the mouth; and dorsum and edges of the tongue (in lines along the longitudinal axis). The lesions are made up of hyperkeratinized epithelium, covered with an adherent pellicle; they are rough to the touch and usually not tender. There may be a reddened and tender zone in the vicinity. The lesions are very chronic and resist all types of local medicaments. Histologically leukoplakia is characterized by acanthosis with hyperkeratosis. Moderate liquefaction degeneration of the basal cell layer occurs. The dermis shows a cellular infiltrate, in some places perivascular, and with some increase in fibrous tissue. The infiltrate is composed of plasma and mast cells and many lymphocytes and connective tissue cells. The elastic tissue is destroyed. When carcinoma supervenes it usually starts as squamous cell epithelioma *in situ* with features of Bowen's disease.

The best critique of leukoplakia the Reviewer has found is that of Montgomery,¹⁹³⁰ which is as follows:

The incidence of epitheliomatous change in leukoplakia is difficult to ascertain because of the various etiologic factors to be considered. McCarthy justly emphasized that the leukoplakia precipitated by syphilis predominates on the tongue, where atrophic

syphilitic glossitis is most frequently the antecedent lesion. Leukoplakia of the buccal surfaces, on the other hand, apparently results most frequently from constant irritation and trauma from smoking or malocclusion. An analysis of different statistics given by MacKee and Cipollaro together with a review of the literature showed that in 20 or 30% of cases leukoplakia of the oral cavity results in malignant change. I can see no difference between leukoplakia or leukokeratosis of the mucous membranes of the mouth and of those of the genitalia, including the vulva and glans penis. Erythroplasia of Queyrat would seem at best only a variant of leukoplakia, being essentially a moist superficial form of the latter. Ręjto's case of erythroplasia of the glabrous skin was an instance simply of moist superficial squamous cell epithelioma. The histologic changes in leukoplakic vulvitis, as distinguished from those of true kraurosis and lichen sclerosis et atrophicus (which has been confused with kraurosis), need not be considered here. I have not been able to demonstrate pathologically any evidence of syphilis in cases of leukoplakic vulvitis. The incidence of epitheliomatous changes in lesions of leukoplakia of the genitalia in my experience has been at least 20%, but if the patients are observed over a long period, as Taussig has done, the incidence of epitheliomatous change may reach 50%. Clinically, as in experimental production of cancer, involution of early leukoplakic lesions in the mouth or on the tongue may be seen after cessation of smoking or the fitting of proper dentures, thus again indicating the reversibility of the process if it has not gone too far.

In contrast with the previously mentioned types of precancerous dermatosis, leukoplakia of the mucous membranes, although frequently starting as an epithelioma *in situ*, may be seen often in the form of an ordinary type of penetrating squamous cell epithelioma, Grades 1 to 4, without much evidence of malignant dyskeratosis or keratinization of individual cells.

Leukoplakic Vulvitis and Kraurosis. Bonney³⁵ clearly defined the 4 stages of the clinical picture of leukoplakic vulvitis which he and Berkeley³⁰ had separated from the other forms of vulvitis and named. Kraurosis is another vulvar affection about which there is great confu-

sion. The designation has been used to include many different conditions which have one feature in common, contraction of the vaginal orifice. A clear differentiation between the two processes, leukoplakic vulvitis and kraurosis, which some authors still feel are different stages of the same entity, was made by Graves and Smith¹⁰⁷ as follows:

Leukoplakic vulvitis is a chronic inflammatory condition of unknown origin characterized in the early stages by marked hyperemia and cellular activity, and in its later phases by marked epithelial hypertrophy, and a thickened, sclerosed, and retracted condition of the subepithelial tissue. The whole of the vulva may be implicated with the exception of the vestibule and orifice of the urethra, which are never affected. It may extend laterally to the folds of the thigh and posteriorly to the external perineum and the skin around the anus. There are four clinical stages:

First stage: reddening, swelling, excoriation, and dryness.

Second stage: retraction with thickening, decrease in size of the greater and lesser lips, and change of color from red to white.

Third stage: cracks and ulcers with discharge and bleeding; tendency to carcinomatous change.

Fourth stage: complete involution; vulval surface smooth, shiny and white; disappearance of labia minora and clitoris from contraction of the subepithelial tissues; cessation of pruritus.

The symptoms are intense pruritus in the second and third stages with pain with acute sensitiveness in the third stage from the exposure of nerve endings in the cracks and ulcers. There are no symptoms in the fourth stage.

Kraurosis vulvæ consists of an atrophic condition of the vulva associated clinically with stenosis of the vaginal orifice and pathologically with certain changes in the dermis. It may involve all the surface of the vulva as far as the skin borders of the labia majora, and the skin of the perineum and anal region. Kraurosis vulvæ is divided into two stages:

First stage: the mucocutaneous surface, red and glistening, is dotted over with small patches varying in color from bright red to purple. The urethral orifice is in a caruncular condition.

Second stage: The mucocutaneous surface becomes yellow like that of a fatty liver. The surface ridges are obliterated. The vaginal orifice is greatly contracted; the labia minora and clitoris disappear; the mons veneris atrophies; the pubic hair breaks off or falls out. The condition is one simply of retraction and thinning. Pruritus is one of the rarest symptoms, the chief complaint being that of dyspareunia. In the first stage, the parts are sensitive, especially to the passage of urine.

Kraurosis. A comprehensive review of this subject by Savill²⁶⁰ has served as the chief basis for this discussion. Breisky³³ was the first to call attention to the condition of contracted vaginal orifice; not all of his cases were associated with deficient ovarian function. Jayle¹³⁴ limited the term kraurosis to the atrophic contraction due to several causes and described a red and white variety as well as kraurosis combined with vulvitis and also with cancer. The red type is accompanied by a reddened urethra, or a caruncle, and with redness of the ducts near the urethra and the vaginal orifice. The lesion of leukoplakia chiefly involves the epidermis, while kraurosis affects the cutis as well and this leads to progressive atrophy and sclerosis. Graves and Smith believe that the clinical and histologic evidence indicate that kraurosis and leukoplakia used in the classic sense are phases of an identical process. Taussig^{295a,b} reserves leukoplakic vulvitis for a state with pruritus, pain on urination, with white areas and subsequent contraction and sclerosis. Kraurosis he defined as the later stage, when the leukoplakic vulvitis has led to obliteration of the labial and preputial folds; thus the condition was seen with deficient ovarian function, in old women or those whose ovaries had been removed. In more than half the cases of leukoplakia vulvitis carcinoma supervenes (39 of 64 cases). He advised vulvectomy as the effective treatment. Montgomery and his associates¹⁹⁴ advocate limiting the term kraurosis to the condition described by Darier (progressive sclerosing atrophy of the mucocutaneous

teguments of the vulva, leading gradually to stenosis of the vaginal orifice, to the disappearance of the labia minora, the hood and the clitoris, and the effacement of the labia majora). The mucosa of the parts involved is smooth, shiny, dry; the color is white, waxy yellow, red or spotted. It may be complicated by leukoplakia and the chief pathologic condition in kraurosis is suppression of the ovarian function by senile involution, by sclerosing atrophy of castration; syphilis plays a rôle in certain cases. Montgomery, Counsellor and Craig conclude: (1) kraurosis is an atrophic process which may possibly lead to a malignant change; (2) leukoplakia of the vulva is a hypertrophic process, definitely a precancerous dermatosis, which frequently results in a malignant state; (3) pruritus vulvæ with lichenification (neurodermatitis) is a benign form of inflammatory dermatosis which does not *per se* result in a malignant change. Adair and Davis⁴ regarded leukoplakia and kraurosis vulvæ as stages of the same disease. Ketron and Ellis¹⁴¹ in an excellent review apparently look on leukoplakia and kraurosis vulvæ as the same process but point out that kraurosis vulvæ (leukoplakia) shows in a considerable percentage of cases peculiar degenerative changes in the connective tissue identical in appearance with those characteristic of their cases of white spot disease. They believe that some cases, at least, which are diagnosed leukoplakia are examples of white spot scleroderma of the vulva. Leukoplakia of the vulva (histologically acanthosis and hyperkeratosis) is probably frequently superimposed on various pathologic processes of the vulva whether primarily of a degenerative or inflammatory nature.

Savill does not believe that kraurosis has symptoms of itself. Any symptoms are due to superimposed infection which occurs from time to time. It occurs in elderly women and in younger women from whom the ovaries have been removed; in both cases preëxisting atrophy prevents the development of the hypertrophic stage with the keratinization seen with leuko-

plakic vulvitis. Savill believes that estrin preparations³⁴² aid by rendering the part more vascular and hence softening the sclerosis and diminishing the contraction. The relief obtained is usually only temporary. Relapse of symptoms occurs when local foci of infection become active. In the late phases, Taussig recommends vulvectomy. Savill has had good results from diathermy.

Tar Cancer—Precancerosis. The carcinogenic properties of tar have been mentioned elsewhere. The specific problem of tar cancer of the lip in fishermen was fully discussed by Shambaugh.²⁶⁵ He found that fishermen in the Massachusetts region are exposed, in the handling and repairing of tarred nets, to the most strongly carcinogenic type of tar, namely horizontal retort gasworks tar. The lips are especially contaminated with the tar because of the frequent practice of holding the tar-smeared needle in the mouth while repairing the nets. On the basis of 8 cases, the author proposes the belief that exposure to tar may be partially responsible for the apparent high incidence of cancer of the lip in fishermen.

Verruca Senilis (Seborrheic Keratosis) and Keratoma Senilis (Senile Keratosis). Freudenthal¹⁹² distinguished verruca senilis from keratosis senilis. His designation apparently referred to keratosis seborrheica and keratosis senilis respectively. Eller and Ryan⁸⁴ and Montgomery^{193d} agree with Freudenthal that these are two distinctly clinical conditions, entirely different in their histologic structure and different in their predisposition to malignant change. Other authors (MacCleod,¹⁸⁰ Williams,³³⁵ Pusey,²⁴⁰ Lain¹⁴⁷) use these terms synonymously. Still others (Unna and Delbanco quoted by Freudenthal) think that the difference, if any, is unimportant and merely an academic question. Sutton and Sutton^{286b} believe that keratoses are intra-epidermal carcinomas of comparatively slow growth rate.

Montgomery (1935) has summarized the pertinent facts relating to these two types of lesion, which we believe are distinctive from the clinical and histopatho-

logic standpoints. Verruca senilis (seborrhoeic keratosis) usually develops in the later decades of life as multiple lesions of various size and occur chiefly in the trunk in the seborrhoeic regions although the face may be extensively affected. They begin as light yellow spots which increase in size, and become pigmented spots which increase in size, and become pigmented, some even bluish brown. A thin greasy scale, readily removed by friction, usually covers the lesions. They have the appearance of being stuck on the skin. Clinically they resemble and may be confused with pigmented nevi (Miescher; Häberlein and Guggenheim: *Arch. f. Dermat. u. Syph.*, 174, 105, 1936), histologically with pigmented basal cell epithelioma.

Histologically these lesions show a characteristic picture, but one resembling dermatosis papulosa nigra (Michael and Seale¹⁸⁶). The features are: nevoid grouping of the epithelial cells; islands of connective tissue which separate the groups; horn cyst formation; thickened horny layer; pigment granules in the basal cells; basophilic degeneration of the connective tissue fibers; mitotic figures rare; slight non-specific inflammation reaction in the cutis; slight edema of upper cutis. Occasionally they may appear in the form of a dry keratotic type which require histologic study for diagnosis. This type of lesion does not show malignant change unless it is subject to irritation and repeated trauma. When they do develop into malignancy the lesion is usually basal cell in type (Pinkus²³¹). Excision, for cosmetic reasons, or if the lesion is in site of irritation, usually gives a good result. Radiotherapy is not a treatment of choice because of the marked degree of differentiation of the individual cells.

Senile keratoses (keratoma senilis) also occurs chiefly in older individuals, but on the backs of the hands and on the face. They may appear anywhere on the body. People exposed to the elements, sun, wind, extremes of weather, are especially prone to develop them. They are accordingly frequent among sailors, farmers, and those who have so-called sailor's skin.

Senile keratoses are discrete, appear as verrucous, brown to grayish keratotic papules, or as ill-defined sealing patches. The scales are dry and adherent and their removal may result in points of bleeding. Evidence of a peripheral zone of erythema together with a sense of palpable induration is, as a rule, indicative of malignancy. Occasionally a senile keratosis develops into a cutaneous horn. The subject of cutaneous horn has been admirably reviewed by Douglas Montgomery.¹⁹² The histologic features are marked hyperkeratosis with or without a tendency to verrucous formation; acanthosis; parakeratosis (variable feature); inflammatory reaction of variable degree in the upper cutis; basophilic degeneration of upper cutis; pigment granules in the basal cell layer not a distinguishing feature; mitotic figures more frequent than in seborrhoeic keratosis; no interlacing of epithelial cells, no horn cysts; but edema of epidermis (basal cell layer). Montgomery believes the histologic features of senile keratoses are less distinctive than in seborrhoeic keratoses. He believes that senile keratoses develop into squamous cell epitheliomas in 20 to 25 % of the cases. Of these, 90 % are squamous cell in type with individual cell keratoses similar to the picture of early Roentgen and radium epitheliomas (Hookey,¹²³ Montgomery and Dörffel,¹⁹⁵ Montgomery^{193a}). This viewpoint is criticized by Sutton, Jr.,^{287b} however.

Treatment of senile keratoses by irradiation with Roentgen rays is illogical, according to Montgomery.^{193f} A good cosmetic result without recurrence may be obtained by thorough fulguration or by light use of the cautery or diathermy.

Xeroderma Pigmentosum. The literature on this subject has been reviewed recently by Beerman and Stokes²⁷ and by Macklin.¹⁷³ Macklin reported a case and presented a consideration of incomplete sex linkage in inheritance of the disease. Loewenthal and Trowell¹⁶⁸ reported 3 cases in an African Negro family, a race presumed to be immune to xeroderma pigmentosum.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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CIGARETTE SMOKE, IRRITATION AND THE THROAT

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SINCE an impressive number of people smoke cigarettes, the effect of cigarette smoke on the human throat is a subject of widespread interest. Despite this, however, most currently published nose and throat text-books either completely ignore the problem or touch upon the theme superficially. It is not surprising, therefore, that among many physicians much unsubstantiated opinion prevails as pseudoscientific belief.

The purpose of this review is to survey the pitfalls of disputed territory and to attempt to arrive at sane conclusions.

Cigarettes and Cigarette Smoking. According to Proetz,¹⁰ the typical American cigarette consists chiefly of American tobacco, with an admixture of Turkish, Egyptian, Greek and other components, cured according to various processes. It is flavored with mixtures of volatile substances which impart to the individual brands their characteristic tastes and aromas. In occasional instances a distinct flavor is imparted by one or another of these ingredients: this occurs with cigarettes containing menthol. The combustion products of burning tobacco leaves which constitute smoke depend not only upon the character of the burning material, but also upon the position of the cigarette while burning; the speed of the puff; the volume of the puff; the frequency of the puffs; the number of puffs in the series; and the humidity of the tobacco and of the room.

The number of puffs taken in smoking a cigarette is highly variable, depending

on both the cigarette smoked and the smoker. Tightly packed cigarettes burn more slowly than those loosely packed and therefore afford more puffs. The main variable, however, is the smoker. While reading, writing, playing cards or similarly occupied, he may take only 3 or 4 puffs from the entire cigarette; again, in moments of nervousness he may smoke with great rapidity. Haggard and Greenberg⁶ observed that a large number of subjects who were habitual smokers, smoking the particular cigarettes under study and with their attention fixed on smoking, showed an average of 17 puffs per cigarette, with extremes of 13 and 22.

The mouth, not the chest, is used to draw in the smoke from a cigarette, and the act is identical with sucking. In taking a puff the pharynx is shut off, the lips are closed about the cigarette and the cavity of the mouth is enlarged by the movement of the tongue. The amount of air that can be drawn into the mouth under these circumstances is limited. Measurements of the volume of air drawn in with a single puff from a cigarette gave an average value of 33 cc., with extremes of 22 cc. and 51 cc. After cigarette smoke is drawn into the mouth, the passage to the larynx is then opened and an inspiration made. The amount of air drawn in corresponds closely with that of a normal inspiration, or about 500 cc. The inhaled air is thus diluted with more than 15 times its volume of fresh air. This diluted air is still further diluted with the stationary air in the respiratory passages, and the

final mixture is exhaled. An occasional smoker, after taking the smoke into the mouth, draws it into the pharynx and exhales it through the nose; the dilution under these circumstances is only to the extent of the volume of air contained in the pharynx and in the nasal passages.

Ballenger and Johnson¹ assert that the products of the combustion of tobacco include carbon dioxide, carbon monoxide, nicotine, ammonia and aldehydes, such as acrolein, formaldehyde, furfural, tars and formic acid. It has not been definitely established which of these various products of combustion is the major factor in a possible irritation of the mucous membrane. Suspected as principle irritants are acrolein, formaldehyde, formic acid and possibly furfural. These products are present in smouldering and burning vegetation. The speed and manner of smoking enter into the rate of production of these possible irritants. In the opinion of Bogen,² fast smoking increases the carbon monoxide and nicotine content of the smoke and to a lesser extent the aldehyde content. "Heat, free nicotine, pyridin and other nitrogenous bases, volatile acids, tarry and phenolic substances and particularly the aldehydes liberated in the smoke, of which furfural and acrolein have been especially condemned, may all contribute to the irritation of the mucous membranes of the smoker." Bogen believes that nicotine plays a small part in local irritation. If the last third of the cigarette is smoked, the nicotine and probably the other constituents of the smoke are greatly increased, which may or may not have an increased irritating effect on the mucosa. Ammonia is given off in the "side stream" but seems to be absent in the "main stream" of the smoke. Cigarette paper gives no harmful products unless nitrate has been added.

Animal Experimentation. In order to insure a satisfactory moisture content some hygroscopic agent is customarily added to cigarette tobaccos. For this purpose glycerin has long been used. In

several publications^{9a,9b,11} it has been indicated that smoke from cigarettes containing diethylene glycol is less irritating than smoke of cigarettes made with glycerin or even devoid of any added hygroscopic agent. Such, for instance, were the observations of Mulinos and Osborne who prepared solutions by drawing smoke from the various types of cigarettes through a small volume of physiologic salt solution, water, oil or Ringer's solution, and then noted the resulting irritation when these smoke solutions were instilled into the conjunctival sac of rabbits. They chose as a criterion of irritation the edema-producing properties of the smoke solution and found the solutions made from diethylene glycol-impregnated cigarettes to be least irritating.

This pronouncement prompted Haag⁵ to repeat the animal experimentation, employing as far as possible the general technic described. All cigarettes were selected of a uniform weight, standard in physical properties, and of the same normal moisture content. Five-sixths of each cigarette was smoked in a conditioned laboratory atmosphere at 85° F. and 45 % relative humidity. The average cigarette was consumed in 8 minutes. The smoke was drawn through 3 cc. of physiologic salt solution, and the smoke solutions of the 2 types of cigarettes were prepared simultaneously and employed experimentally the same day.

In performing the animal observations, Haag used 3 drops of the smoke solution, instilling them into the left eye of the rabbit, the right eye serving as a control. As evidence of the degree of irritation provoked, the objection of the animal and the blepharospasm, as well as the extent and duration of the hyperemia and edema of the conjunctiva were tabulated at regular intervals of several minutes. It appears from Haag's results that there was no significant difference, either as to intensity or duration, in the irritation produced by the instillation into the rabbit eye of the 2 smoke solutions studied. He concludes that when aqueous smoke

solutions, obtained from diethylene glycol-treated and glycerin-treated cigarettes, were instilled into the conjunctival sac of rabbits, no differences in the irritating properties of the 2 types of cigarettes were observed, as judged by the appearance of hyperemia, edema, blepharospasm and the objection of the animal.

McNally⁸ and his associates, using hyperemia as the criterion of irritation, also studied the irritating properties of smoke from tobacco treated with glycerin and diethylene glycol. Finding no significant difference between the smoke from the 2 types of tobacco or between either of these and the smoke from plain tobacco, they declare: "Our own work is in complete harmony with the view that no significant difference exists. Many of the authors cite the difficulty in interpreting the observations, both clinical and laboratory, yet Mulinos and Osborne were able to note 8 different degrees of edema! If differences in effects are so slight as to be difficult to classify by the majority of observers, how can such differences have *any* practical significance?"

Weatherby,¹² using the trypan blue technique involving intradermal injections in rabbits' ear, also found no difference between the 2 types of cigarette smoke.

Clinical and Laboratory Investigations. Flinn⁴ enumerates a number of difficulties associated with a strictly clinical study of the effect of cigarettes. He states that in a study of the effect of smoking on the mucous membrane of the nose and throat there is no scale by which one can express the degree of congestion; that one must depend on personal impressions which cannot be carried with exactitude to another examination 1 week later; and that one cannot take tissue and compare it in a colorimeter with a known standard so that it can be expressed in terms that will correspond to the determinations made by another observer. Having established these premises, Flinn veers away from their soundness and concludes from clinical observations that the smoking of diethylene glycol-treated cigarettes

seldom causes irritation, and that indeed it actually appears to be followed by an ameliorating effect upon an irritated throat and tongue.

In an effort to determine by clinical means the presence of any irritating properties of the hygroscopic agent used in cigarettes, Ballenger and Johnson observed 100 subjects. The cigarettes were identical in composition except in the hygroscopic agent used. One lot contained glycerin, a second diethylene glycol, and a third had no hygroscopic agent. They conclude that the hygroscopic agent used in cigarettes is not a factor of importance in producing symptoms or in producing objective evidence of irritation of the nasal or throat mucosa.

In a study of cigarette smoke and its effect upon the respiratory tract conducted by Proetz, 26 subjects were observed by 8 trained physicians. The observers were instructed to examine the throats of the subjects and to classify their findings according to the following: (a) throats having no suspicion of any inflammatory reaction, so-called normal throats; (b) throats showing minor signs of irritation or inflammation of no clinical importance; (c) throats definitely red and inflamed; and (d) severe sore throats, of the type usually associated with fever and other systemic symptoms. After an inquiry into the reliability of simple comparative clinical observations of the pharyngeal mucous membrane he came to the conclusion that "Regarding the reliability of simple clinical observation as a basis for statistical studies of the pharynx, even under the best conditions and with the problem clearly defined in the mind of the examiner, we find a diversity of opinion (*i. e.*, among 8 trained medical observers) reaching 79%." Just what are the objective changes produced in the mucosæ by the protracted action of cigarette smoke was not determined. Belief is expressed that it is not at all certain that they may be classified in terms of color, or even that progressive irritation results in progressively heightened color.

Holck and Carlson⁷ maintain that the method employed by Mulinos and Osborne is not quantitative and that the method used by Flinn is also not quantitative. It is known that within physiologic limits irritation of the mucous membranes of the mouth give rise to increased salivation. Tobacco smoke is an irritant known to stimulate salivary flow. If glycerin added to tobacco increases the irritating properties of the smoke, one would expect a greater flow of saliva from the smoking of tobacco treated with this hygroscopic agent, and if diethylene glycol markedly decreases the irritative properties, the reverse would be expected. With these considerations in mind, experiments were undertaken to measure the salivary responses of 26 men and 2 women. This method of measuring the degree of irritation caused by smoke was employed because the buccal cavity is normally the place of entrance of tobacco smoke, and because it gives an objective quantitative measurement.

The average responses of the 28 subjects to the 3 kinds of cigarettes—glycerin-treated, diethylene glycol-treated and hygroscopic agent-free—agreed very closely, so that there was not the slightest indication that one cigarette was more irritating than another. The data of Holck and Carlson give no indication that cigarettes can be classified consistently as to the irritating quality of the smoke by supposedly normal human beings. In many instances the same kind of cigarette was at one time called mild and at a subsequent period pronounced irritating by the same person. It is believed that a method for determining the irritating properties of cigarettes which relies solely upon the opinions of ordinary smokers cannot be called reliable.

In order to eliminate some of the disadvantages inherent in methods employed elsewhere—namely, (a) efforts to acquire data from mechanical or robot smokers consisting of glass tubes and flasks which, at best, provide neither the human subject nor the precise conditions under which

human beings smoke; (b) the unsatisfactory conclusions that can be drawn from experiments on rabbits' eyes, an anatomic site which is not comparable to the human throat; and (c) the lack of reliable information that can be obtained from clinical observation of the human throat—Fabricant³ measured the effect of cigarette smoke on the normal, physiologic range of the pH of the mucous membrane of the human throat. A silver-silver chloride glass electrode in conjunction with an electrometer was employed. In essence, studies of the pH of the mucous membrane of the throat apply a laboratory procedure in a clinical environ. The subjects were 100 men and women with clinically normal throats.

Three kinds of cigarettes were used in the experiments: cigarettes containing glycerin, diethylene glycol, and those without a hygroscopic agent. In the conduct of the experiments the speed and volume of the puff, the frequency and number of puffs and the position of the cigarette while burning were left entirely to each smoker's preference and habits. Some of the smokers discarded a cigarette after a half-dozen puffs; the majority, however, discarded it much later. While some inhaled deeply, others did not. Each smoker was cognizant of the type of cigarette he was smoking. No attempt was made to alter in any way a smoking technique which may be called the average smoking habit.

The effect of smoking 2, and even 3, dissimilar cigarettes within a prescribed period indicated no abnormal alteration of the normal, physiologic pH of the throat. The smoking of a glycerin-treated cigarette did not disturb the normal, physiologic pH range of the mucous membrane of the throat. A comparison of the effect of the glycerin-treated cigarette and that of the diethylene glycol-treated cigarette failed to show any difference between them. Further, there was no difference between the diethylene glycol-treated cigarette and the cigarette devoid of a hygroscopic agent, nor was there any difference between the effect of the gly-

cerin-treated cigarette and that of the hygroscopic agent-free cigarette. Although in this series of 100 subjects there was no incompatibility between the smoking of cigarettes and the normal, physiologic pH values for the throat, it is conceivable that a tobacco-sensitive or tobacco-allergic person or one with an acutely inflamed throat might show alterations in the pH range.

The question as to the possible harmful effects of smoking cigarettes containing menthol has been investigated by Haggard and Greenberg. The amount of menthol in mentholated cigarettes on the American market was found to range between 1 and 2 mg. per cigarette. Approximately one-half the menthol in the cigarette is lost by combustion; the other half appears in the smoke. On inhalation of the smoke approximately 70% of the menthol is absorbed, an amount so small as to be innocuous. Five minutes after a subject has smoked a mentholated cigarette, menthol cannot be found in the saliva or in the expired air.

Comment. At one time or another various components of cigarettes, cigarette

smoke and tobacco combustion—heat, nicotine, pyridine and pyridine derivatives, carbon dioxide, carbon monoxide, ammonia, the aldehydes, acrolein, formaldehyde, formic acid, furfural, tarry and phenolic substances, and cigarette paper—have been declared responsible for throat irritation. All investigators in the field of tobacco research are agreed that it has not been definitely established which of these various components is the major factor.

Methods for determining the irritating properties of cigarettes which rely solely upon the opinions of ordinary smokers cannot be called reliable. Clinical studies of the effect of cigarette smoke on the human throat for comparative purposes are also unreliable. Unsatisfactory conclusions are drawn from experiments on rabbits' eyes, an anatomic site which is not comparable to the human throat.

In order to insure an adequate moisture content some hygroscopic agent—glycerin or diethylene glycol—is customarily added to cigarette tobaccos. Preponderant investigative opinion indicates that there are no differences in the irritating properties of the 2 types of cigarettes.

REFERENCES

- (1.) Ballenger, H. C., and Johnson, V. H.: *Arch. Otolaryngol.*, 25, 75, 1937.
- (2.) Bogen, E.: *California and West. Med.*, 45, 342, 1936.
- (3.) Fabricant, N. D.: *Arch. Otolaryngol.*, 37, 404, 1943.
- (4.) Flinn, F. B.: *Laryngoscope*, 45, 149, 1935.
- (5.) Haag, H. B.: *J. Lab. and Clin. Med.*, 22, 341, 1937.
- (6.) Haggard, H. W., and Greenberg, L. A.: *Arch. Otolaryngol.*, 33, 711, 1941.
- (7.) Holck, H. G. O., and Carlson, A. J.: *Proc. Soc. Exp. Biol. and Med.*, 36, 302, 1937.
- (8.) McNally, W. D., Bergman, W., and Foster, R. H. K.: *Illinois Med. J.*, 87, 250, 1945.
- (9.) Mulinos, M. G., and Osborne, R. L.: (a) *Proc. Soc. Exp. Biol. and Med.*, 32, 241, 1934; (b) *New York State J. Med.*, 35, 590, 1935.
- (10.) Proetz, A.: *Ann. Otol., Rhinol. and Laryngol.*, 48, 176, 1939.
- (11.) Wallace, G. B., Reinhard, J. F., and Osborne, R. L.: *Arch. Otolaryngol.*, 23, 306, 1936.
- (12.) Weatherby, J. H.: *J. Lab. and Clin. Med.*, 25, 1199, 1940.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 19, 1946

Di-isopropyl Fluorophosphate, a New Irreversible Anticholinesterase Agent.

GEORGE B. KOELLE, PH.D., 1st Lt., M.A.C., and ALFRED GILMAN, PH.D., MAJOR, SN.C. (Med. Res. Lab., Chem. Warfare Service, Edgewood Arsenal, Md.). The alkyl fluorophosphates, first synthesized by Lange and von Krueger and later studied by British and American investigators as potential chemical warfare agents, have been shown to act as irreversible anticholinesterase agents. Certain aspects of the pharmacology of di-isopropyl fluorophosphate (DFP) have been investigated to provide a background for its clinical trial in the treatment of myasthenia gravis and glaucoma.

When rats were given intramuscular injections of DFP, the relative degrees of inhibition of the cholinesterases of brain, muscle, red blood cells and serum were found to correspond fairly closely to their *in vitro* sensitivities. The regeneration of serum and red cell cholinesterase required about 2 weeks in this species, while about 100 days were necessary for the restoration of brain and muscle cholinesterase. Symptomatology and serum and red cell cholinesterase activity were followed in dogs and monkeys following the administration of single doses of DFP. It was concluded that measurements of the degree of inhibition of serum or red cell cholinesterase do not provide a reliable indication of the activity of the enzyme in the tissues.

Chronic toxicity studies were conducted on dogs receiving repeated high doses, and dogs, monkeys and rats receiving repeated moderate doses of DFP over periods of from 3 to 6 months. Both dogs on the high doses developed cardiospasm, urinary incontinence and paralysis of the hind legs.

Bronchopneumonia occurred in 3 of the 4 monkeys, terminating fatally in 1. In neither of these species did abnormalities appear in routinely performed red cell counts, white cell counts, differential counts, or blood sugar, plasma NPN, serum protein, or hepatic function determinations. The rats developed no effects attributable to the drug.

The Influence of Di-isopropyl Fluorophosphate on the Normal and Glaucomatous Eye.

IRVING H. LEOPOLD, M.D., D.Sc. (Department of Ophthalmology, Hosp. Univ. of Penna.). The length, speed and intensity of action with di-isopropyl fluorophosphate was determined on the eyes of the rabbit, cat, dog and man. Di-isopropyl fluorophosphate was found to be more prolonged in its action than any other known miotic agent in the concentrations used. Studies on the denervated iris of the cat's eye disclosed that this agent worked solely by its anticholinesterase activity. In the concentrations used on the normal eye this agent produced considerable ciliary spasm, false myopia and subjective symptoms related to the ciliary spasm. The rate of diffusion of fluorescein and inulin from the blood stream into the anterior chamber of the normal rabbit eye and into the rabbit eye under the influence of DFP was determined. The results of the trial of di-isopropyl fluorophosphate in glaucomatous eyes showed that this agent has definite potentialities in the medical treatment of glaucoma.

A Study of Carbon Dioxide Assimilation in the Rat With Isotopic Carbon. ADELAIDE M. DELLUVA, M.S., and D. WRIGHT

WILSON, PH.D. (Dept. of Physiol. Chem., Univ. of Penna.). The utilization of carbon dioxide by animal tissues *in vivo* was studied. An adult female rat was injected intraperitoneally with isotopic sodium bicarbonate solution. The injections of the isotonic solution were made at 1 hour intervals for a period of 18 hours with 5 ml. of solution each time. The rat was killed by severing the carotid artery $\frac{1}{2}$ hour after the last injection. Analyses were made of the pooled urine, pooled feces, long bones of the fore and hind legs, and fat-free proteins of the liver, muscle, and kidney (the kidney fraction included the spleen and part of the small intestine). Isotope was found in the carbonate of the urine, carbon of the urea, carbonate of the bone, alpha-carboxyl carbon of the glutamic acid, the carboxyl carbons of aspartic acid, and amidine carbon of arginine. There was very little isotope in the carbonate of the feces. The position of the labelled carbon in the arginine coincided with what would be expected from an operation *in vivo* of the ornithine cycle for urea formation. The isotope location in the glutamic and aspartic acids was in accord with the positions of tagged carbon to be expected in the products of transamination of isotopic oxalo-acetic and alpha-ketoglutaric acids formed during the assimilation of labelled carbon dioxide.

The Passage of Endogenous Estrogen Across the Parabiotic Union in Rats. ISOLDE T. ZECKWER, M.D. (Dept. of Pathol., Univ. of Penna.). When an ovariectomized rat, A, is united in parabiosis with a litter-mate female rat, B, the

pituitary of A hypersecretes FSH which passes to Rat B, causing secretion of estrogen by the ovaries. In the early stages, the vagina and mammary glands of A are atrophic; the vaginal epithelium of B, cornified. In less than 1 month, estrogen in B releases LH from the pituitary of B, with development of many large corpora lutea. At this stage, estrogen passes from B to A, resulting in cornification of vaginal epithelium in A, and coincident with this, the vaginal epithelium of B changes from cornification to mucification. It is known (Biddulph *et al.*) that when exogenous estrogen is injected into 1 of a pair of rats, 40 times the dose that is effective in the single rat is required to permit passage of estrogen across the parabiotic union. Consequently the level of endogenous estrogen in B must be very high at the time that it passes to A. Therefore, progesterin from the corpora lutea has not resulted in lowering the blood level of estrogen. Mucification of vaginal epithelium is known not to be a positive effect of progesterin, as progesterin alone causes no histologic change in vaginal epithelium, but is due to the effect of estrogen antagonized by progesterin (according to Korenchesky and Hall, in the proportion of 1500 γ progesterone to 1 γ estrone). It is concluded that in the parabiotic rats, this modification of the effect of estrogen by progesterin must take place in the reacting tissues, not in the blood stream. After a month or longer, these changes are replaced by the well-known atrophic changes in A and the effects of constant estrogen without progesterin in B which last many months.

BOOK REVIEWS AND NOTICES

MEN WITHOUT GUNS. Text by DEWITT MACKENZIE, War Analyst of The Associated Press. Descriptive Captions by MAJOR CLARENCE WORDEN, Medical Department of the United States Army. Foreword by MAJOR GENERAL NORMAN T. KIRK, Surgeon General of the United States Army. Pp. 152; 137 ills. Phila.: Blakiston, 1945. Price, \$5.00.

THIS book records in words and pictures the services of our doctors, nurses, and enlisted men on the battlefields and in the

hospitals of Europe and Asia. A dozen American artists contributed to the notable series of paintings. These artists are: John Stewart Curry, Fred Shane, Manuel Tolegian, Ernest Fiene, Franklin Boggs, Robert Benney, Joseph Hirsch, Lawrence Beall Smith, Howard Baer, Francis Criss, Peter Blume, and Marion Greenwood.

The book is filled with the exciting drama of modern warfare and is a valuable record of the men who fought without guns for the second World War. D. C.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MAY, 1946

ORIGINAL ARTICLES

NUTRITIONAL MACROCYTIC ANEMIA, ESPECIALLY IN PREGNANCY RESPONSE TO A SUBSTANCE IN LIVER OTHER THAN THAT EFFECTIVE IN PERNICIOUS ANEMIA*

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RECENTLY we have studied 4 patients with nutritional macrocytic anemia who showed no response to the parenteral administration of adequate doses of liver extracts regularly effective in Addisonian pernicious anemia. Three of these patients immediately thereafter responded to liver extracts given orally; the 4th, to a larger amount of the same preparation given parenterally. Since this indicated response to a substance other than the hematopoietic factor presumably common to all liver extracts effective in Addisonian pernicious anemia, it seemed desirable to present these cases and to review apparently similar cases, which so far have been reported only in the foreign literature.

One of us^{8,14} in 1929 postulated that the hematopoietic factor effective in Addisonian pernicious anemia is normally formed by the interaction of a gastric (intrinsic) and a food (extrinsic) factor. It was

demonstrated that in Addisonian pernicious anemia the intrinsic factor is usually absent. Evidence obtained later^{9,45} suggested that in other types of macrocytic anemia also, the specific factor in liver extract is lacking as a result of absence of food (extrinsic) or of gastric (intrinsic) factor; of defective absorption of their reaction product from the gastro-intestinal tract; or of some combination of these pathogenic factors. Thus, the unitarian concept was set forth^{10,11} that pernicious and related macrocytic anemias had in common the characteristic of responding to oral or parenteral administration of a single active principle in liver extract. The extract which was employed at that time was a fraction of liver soluble in 70% alcohol but precipitated when the concentration of the alcohol was raised to 95% by volume; that is, Fraction G of Cohn, Minot and their associates.¹⁵ Consistent

* The expenses of this investigation were defrayed in part by the J. K. Lilly gift to the Harvard Medical School.

† Commonwealth Fund Fellow.

with this hypothesis appeared to be the regularity of response to parenteral administration of such relatively crude liver extracts observed in Addisonian pernicious anemia,^{24,46} in the macrocytic anemia of the tropics^{36,61} and of tropical^{12,30,50} and non-tropical sprue,⁴¹ and in macrocytic anemia associated with abnormalities of the gastro-intestinal tract,^{2,49} dietary (extrinsic factor) deficiency,²⁷ pregnancy,^{34,42} and fish tapeworm infestation.⁶ However, since 1938 there have appeared in the foreign literature scattered reports of cases of macrocytic anemia which have responded poorly, or not at all, to the parenteral administration of the refined liver extracts that first became generally available at about that time. These patients have subsequently responded either to less refined liver extracts given parenterally or, failing in this, to liver or other preparations given orally.

Review of Literature. The clinical observations on such differences in therapeutic activity of liver extracts of various degrees of refinement were foreshadowed in 1937 by the results of experimental studies in monkeys, made by Wills, Clutterbuck and Evans.⁶⁰ These workers showed that in contrast to a relatively crude liver extract, Campolon,²⁶ a purified liver extract, for example Anahaemin,^{16,53} was therapeutically ineffective. Napier and his associates³⁶ in 1938 reported that of 15 patients with tropical macrocytic anemia which they observed in India 3 failed to respond to parenterally administered Anahaemin, but subsequently responded to parenterally administered Campolon. Wills and Evans⁶¹ in the same year reported 26 cases, also from India, in which Anahaemin was ineffective but in which there subsequently occurred a response to Campolon or to the oral administration of Marmite (autolyzed yeast). Later, Napier³⁵ reported that Anahaemin, if given in massive doses, would sometimes produce a response, although it was never as effective as Campolon. Trowell⁶¹ reported that his patients in Uganda seemed to require more Anahaemin or more Campolon than did patients with pernicious anemia, and he regarded liver given by mouth as the treatment of choice. On the other hand, Foy and Kondi²⁴ and

Fairley²³ found that nutritional macrocytic anemia in Macedonia responded equally well to Anahaemin and to cruder preparations for parenteral use, such as Campolon. Rodriguez-Molina⁴⁰ observed a patient with tropical macrocytic anemia in Puerto Rico who responded well to autolyzed yeast after showing no response to liver extract given intramuscularly.

In addition to the tropical macrocytic anemias, there have been cases of macrocytic anemia of pregnancy in the temperate zone, which have not responded satisfactorily to parenterally administered refined liver extract. Ungley⁶² in 1938 published, without specific comment, the chart of a patient who failed to respond to a 10-day course of Anahaemin, but who subsequently showed a striking response to oral therapy with a combination of iron, Marmite, orange juice, liver and kidney. In 1942 Davidson, Davis and Innes¹⁷ reported 16 cases of megaloblastic anemia of pregnancy, 10 of which were temporarily refractory to refined and crude liver extracts, such as Anahaemin and Campolon, administered parenterally for periods varying from 11 days to several months. In the same year Miller and Studdert,³¹ in reporting 23 cases of pernicious anemia of pregnancy, stated that 1 patient responded to a diet rich in vitamin B after showing no response to "pure" liver extract given parenterally; and that 5 patients responded to raw liver, 2 of them after failing to respond to Anahaemin, given parenterally. Unfortunately individual cases were not described in detail. Fullerton²⁵ in 1943 reported 3 cases of macrocytic anemia of pregnancy "of interest because there was little or no improvement in the blood level after liver extracts given parenterally, but rapid regeneration occurred when this treatment was supplemented by the ingestion of whole liver." Scrutiny of the hematologic data, however, indicates that such a clear cut interpretation of the results is difficult, as the writer himself admits. It should be emphasized that in contrast to these investigators who claim to have found that parenterally administered refined liver extract was therapeutically inadequate in cases of pernicious anemia of pregnancy, there are others^{1,29,34,42,44} who have found this treatment satisfactory in the majority of their cases. The literature on the subject of the anemias of pregnancy has re-

cently been ably reviewed by Callender⁷ and by Elliott.²¹

Finally, there have been reported a few miscellaneous cases of nutritional macrocytic anemia in the temperate zone with atypical response to liver extract therapy. Nielsen³⁸ in 1941 stated that he had studied 4 cases in Denmark which did not respond to liver extract given parenterally or to stomach preparations given by mouth, but which did respond to orally administered liver extract. Analysis of these cases reveals that only 1 was adequately controlled. This patient responded to the oral administration of autolyzed yeast after showing no response to parenterally administered refined liver extract, Pylorin (desiccated hog stomach pylorus), lactoflavin and Ventriculin, N. N. R. Fullerton²⁵ mentions briefly 3 cases of macrocytic anemia associated with steatorrhea, which were refractory to extracts administered parenterally but responded rapidly when they were given whole liver without other alteration in the diet. Of particular interest is the report by Davidson, Davis and Innes¹⁸ in 1943 of 6 cases of severe idiopathic macrocytic anemia with megaloblastic sternal marrow, all of which were refractory to liver extract given parenterally for periods of from 4 to 10 weeks, but eventually recovered. Orally administered liver was not tried in these patients, but recently Davis and Davidson^{19,20} have demonstrated most convincingly in 5 instances that such refractory anemias respond at once to orally administered "proteolyzed liver." In retrospect there is also perhaps therapeutic significance in the report by Bomford and Rhoads⁵ of "spontaneous remissions" in 6 cases of refractory anemia, in 3 of which (Cases 18, 19 and 21) these remissions occurred during treatment with orally administered liver or liver extract.

As a group, these cases of nutritional macrocytic anemia described by other authors seemingly failed to respond to refined or in some instances to crude liver extracts given parenterally, and thus differed from cases of Addisonian pernicious anemia. Unfortunately some of the reports lacked such pertinent hematologic data as reticulocyte counts, or such essential therapeutic controls as demonstration of fail-

ure to respond to parenterally administered liver extract immediately preceding response to an orally administered product. Moreover, therapy often included several agents given simultaneously, so that it is difficult to conclude which was effective. The present report of observations on 4 patients with macrocytic anemia supplements a preliminary communication⁵⁷ and appears clearly to demonstrate response to a hematopoietic substance other than that effective in Addisonian pernicious anemia, whether given by the oral or by the parenteral route.

Methods. On the basis of previous experience with pernicious anemia,^{8,11} one or more successive 10-day periods of daily administration were considered adequate to establish the hematopoietic activity of a test preparation, chiefly by the absence or presence of a significant reticulocyte response.^{8,32} The percentage of reticulocytes in 1000 red blood cells was determined daily from blood films vitally stained with brilliant cresyl blue and counterstained with Wright's stain. Complete blood counts, including hematocrit and corpuscular indices, were made on alternate days from 5 cc. of venous blood placed in a bottle containing 6 mg. of ammonium oxalate and 4 mg. of potassium oxalate crystals. During the periods of critical observation the patients were kept on diets containing no meat, fish, eggs, liver or hematopoietic substances other than those under test. The results of these observations are presented graphically in Figures 1 to 5.

Discussion. *Evidence that the basic nutritional deficiency differs from that in Addisonian pernicious anemia.* All 4 of our cases of nutritional macrocytic anemia, like others reported,^{7,35,58} possessed in common certain characteristics which distinguish them from cases of Addisonian pernicious anemia. The most important features seemed to be a history of marked dietary inadequacy, especially with respect to meat, and the presence of free hydrochloric acid in the gastric contents. Additional distinguishing characteristics were absence of neural manifestations and

of atrophy of lingual papillæ; less macrocytosis, anisocytosis and poikilocytosis of the red blood cells than is usual in pernicious anemia; an unusually low percentage of reticulocytes; and a normal icterus index. Other observers have noted that the bone marrow in such cases is megaloblastic^{20,35} and that maintenance liver extract therapy is not required.¹⁸ Our patients have not been followed sufficiently long to permit definite conclusions, but the 3 patients who have taken no liver extract for over a year have suffered no relapses.

In Case 2, the presence of free hydrochloric acid in the gastric juice and the absence of response to daily therapy with 1 cc. of Reticulogen-Lilly and 4 U. S. P. units (injectable) of Liver Injection (Crude), U. S. P.-Wilson eliminated the possibility of typical Addisonian pernicious anemia (Fig. 2). In this case, too, the blood picture and the hemorrhagic phenomena were suggestive of aplastic (refractory) anemia; but here again there was a striking response to orally administered Liquid Extract of Liver, U. S. P.-Valentine, 1 U. S. P. unit (oral) daily.

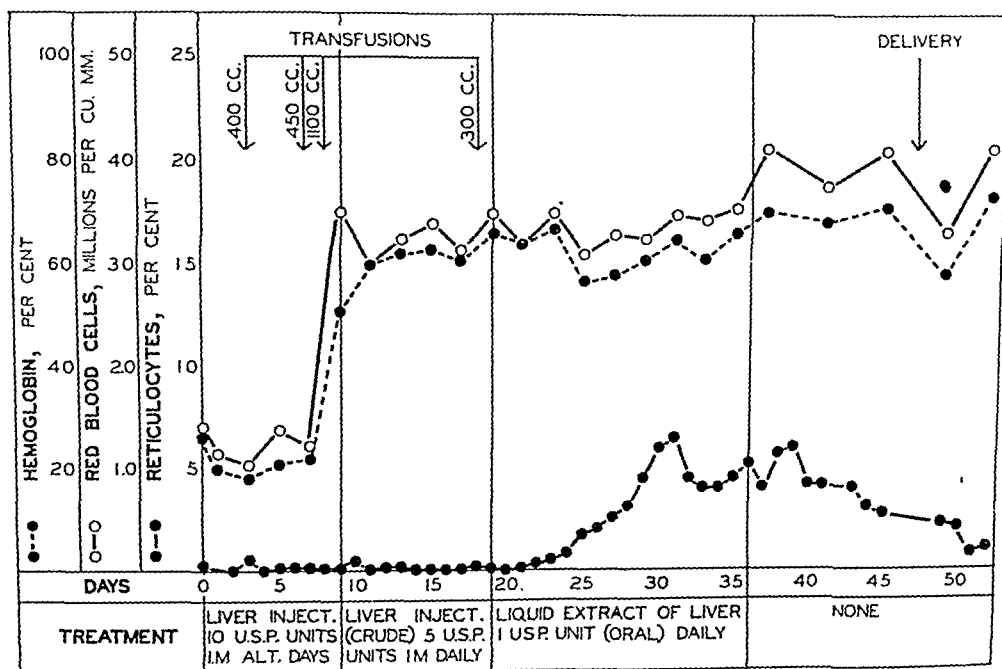


FIG. 1.—(Case 1.) Nutritional macrocytic anemia of pregnancy. Response to orally administered Liquid Extract of Liver, U. S. P.-Valentine after failure to respond to parenterally administered Liver Injection, U. S. P.-Lederle and Liver Injection (Crude), U. S. P.-Wilson.

Case 1 was fairly typical of pernicious anemia of pregnancy. When there was no response to several U. S. P. units (injectable) daily, first of Liver Injection, U. S. P.-Lederle⁵⁴ and then of Liver Injection (Crude), U. S. P.-Wilson,⁵⁵ the diagnosis of pernicious anemia was excluded, and aplastic (refractory) anemia seemed likely (Fig. 1). Subsequently, however, there was a prompt response to orally administered Liquid Extract of Liver, U. S. P.-Valentine,^{37,39} 1 U. S. P. unit (oral) daily.

Because the daily injection of a single U. S. P. unit is sufficient to produce a striking hematologic and clinical remission in uncomplicated Addisonian pernicious anemia,⁵⁴ the therapeutic failure of these potent liver extracts when given parenterally clearly indicates that the nutritional deficiency in these patients did not consist in a lack of that active principle of liver extract which is effective in Addisonian pernicious anemia.

According to the hypothesis of Strauss

and Castle,⁴⁵ deficiency of the active principle of liver extract which is effective in Addisonian pernicious anemia is the result of lack of either the so-called food (extrinsic) factor or the gastric (intrinsic) factor, or is due to defective absorption of their reaction product from the intestinal tract. Therefore, because the macrocytic anemia in our patients failed to respond to the parenteral administration of liver extracts effective in Addisonian pernicious anemia, it is clear that deficiency of extrinsic or intrinsic factors or defective absorption of their reaction product is not

the basis of this report differs from that in Addisonian pernicious anemia, what is the explanation of the hematopoietic activity exhibited by the orally administered Liquid Extract of Liver, U. S. P.-Valentine? Two obvious possibilities present themselves: (1) that the administration of the material by the oral route is necessary for the elaboration of some active principle different from that effective in Addisonian pernicious anemia; or (2) that an effective amount of the different active principle is already present in the prepara-

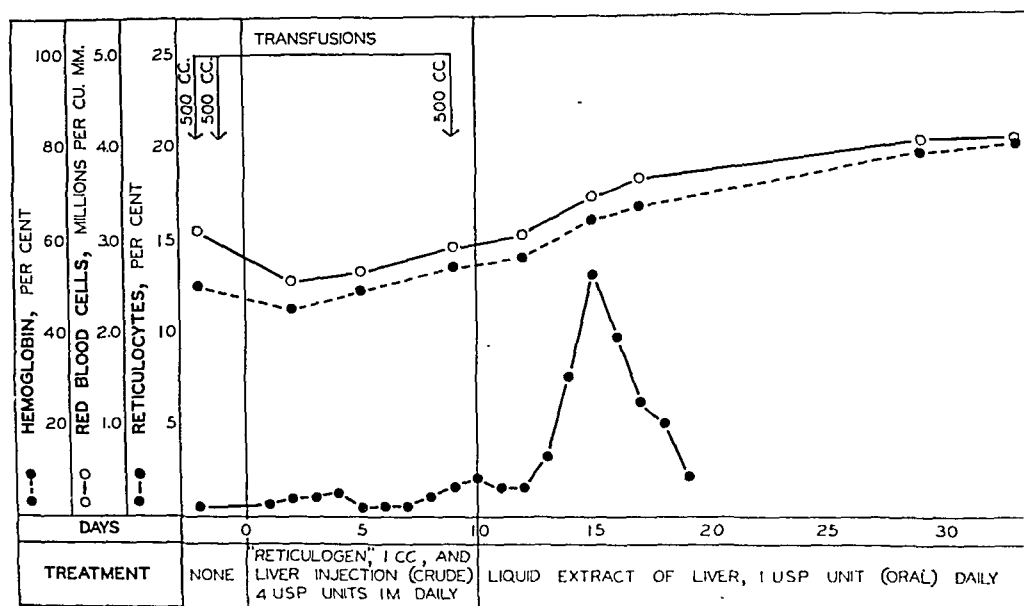


FIG. 2.—(Case 2.) Nutritional macrocytic anemia. Response to orally administered Liquid Extract of Liver, U. S. P.-Valentine after failure to respond to parenterally administered Reticulogen-Lilly and Liver Injection (Crude), U. S. P.-Wilson.

its cause. Consequently the unitarian theory of the etiology of macrocytic anemias of nutritional deficiency, which has been advanced by Str uss and Castle, does not apply to the patients presented in this report. This conclusion was first clearly reached in 1938 by Napier and his associates^{35,36} and by Wills and Evans⁶¹ for certain macrocytic anemias occurring in the tropics, which failed to respond to refined liver extracts given parenterally.

Evidence concerning the nature of the hematopoietic agent. If, then, the nutritional deficiency of the 4 patients forming

tions administered orally but not in those administered parenterally.

The observations in Case 3 were accordingly designed to discover a liver extract which was orally effective in nutritional macrocytic anemia of the type under study and which could also be given parenterally. Based on previous experience in pernicious and related macrocytic anemias,^{12,46,47,48} a "special liver preparation" was now employed. This contained in 5 cc. as a suspension-solution, at pH 6.8, 1.25 gm. of powdered Liver Extract-Lilly, N. N. R.³⁷ Case 3 resembled Case 1

in clinical and hematologic aspects except that delivery took place on the day that the observations were begun. In a first period of 8 days the patient was given daily injections of 5 cc. of the special liver preparation without detectable effect* (Fig. 3). Owing to the serious condition of the patient it was then considered advisable to discontinue parenteral therapy. Beginning on the 9th day, therefore, the patient was given daily, by oral administration, 51 cc. of the same special liver preparation, containing 12.75 gm. of

ceivably delay or failure of response to material administered during the first period could have been caused by an infection responsible for the fever which was present from the 4th to the 16th day. However, because no locus of infection was demonstrable, the fever was probably due to the anemia and in any case was present during as well as before the period of active hematopoietic response.

The observations in Case 3 indicate that the special liver preparation was active on oral administration. Thus, the

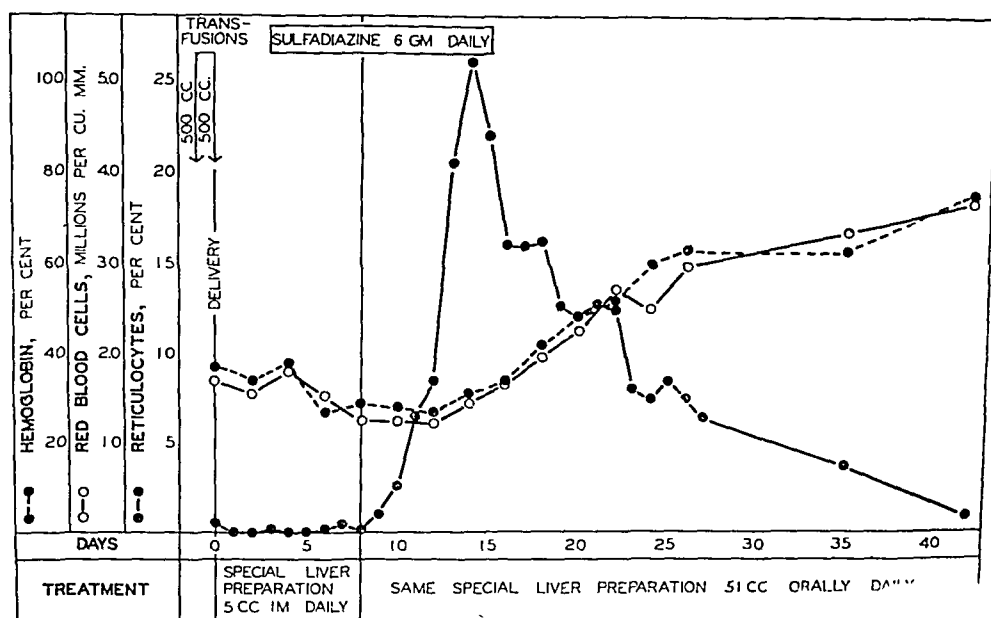


FIG. 3.—(Case 3.) Nutritional macrocytic anemia of pregnancy. Response to orally administered special liver preparation (suspension-solution of Liver Extract-Lilly, N. N. R.) after failure to respond to the same preparation given intramuscularly.

powdered Liver Extract-Lilly, N. N. R.,³⁷ or the equivalent of 1 U. S. P. unit (oral). Under this therapy the reticulocytes increased rapidly and on the 7th day reached a peak value of 26.2%. It is considered unlikely that this rise was due to a delayed response to the material administered parenterally during the first period because in uncomplicated pernicious anemia at least, large reticulocyte responses almost never begin as late as the 10th day,³² especially with parenteral therapy. Con-

suspension-solution of Liver Extract-Lilly, N. N. R.,³⁷ containing material soluble in 70% but insoluble in 95% alcohol by volume,¹⁵ like the simpler aqueous extract,³⁹ Liquid Extract of Liver, U. S. P.-Valentine³⁷ (Cases 1 and 2), was shown to supply a hematopoietic factor different from that effective in Addisonian pernicious anemia. The fact that this identical special liver preparation was active on oral administration but not on injection suggested the first possibility referred to above; namely,

* Tests of the potency of this preparation in patients with Addisonian pernicious anemia showed that 2 cc., when injected daily, were equivalent to about 1 U. S. P. unit (injectable) of certain official U. S. P. preparations.

that in order to become active hematopoietically, the liver extract requires access to the gastro-intestinal tract, perhaps there to be acted on by some secretion in a manner analogous to the extrinsic-intrinsic factor mechanism in Addisonian pernicious anemia. Consistent with this idea was the demonstrated presence of hydrochloric acid in the gastric contents of this patient as well as of the other patients reported here. The second possibility, however, offered the simpler explanation: that a greater amount of the unknown active

preparation given was of prime importance. This patient had nutritional macrocytic anemia with a history of prolonged dietary inadequacy. Free hydrochloric acid was present in the gastric contents. Addisonian pernicious anemia was excluded by the absence of hematopoietic response, in an initial 10-day period, to the daily intramuscular injection of 2 cc. of the special liver preparation, the suspension-solution of Liver Extract-Lilly, N. N. R., estimated to be equivalent in hematopoietic activity to about 1 U. S. P.

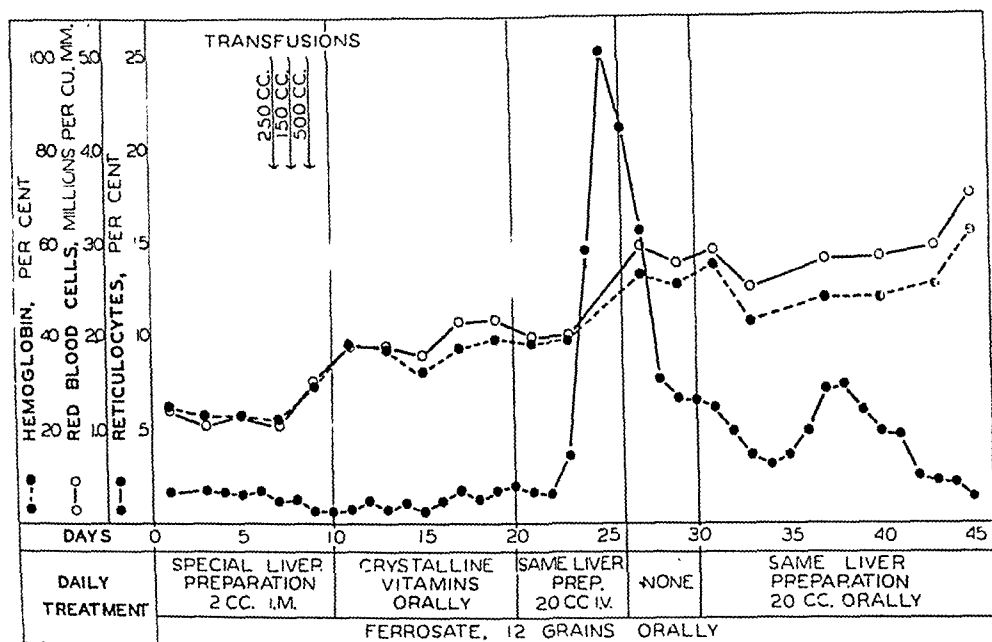


FIG. 4.—(Case 4.) Nutritional macrocytic anemia. Failure of response to various pure components of the vitamin B complex and accessory nutritional substances, including biotin, *L. casei* factor and pyridoxal. Response to daily parenteral administration of 20 cc. of special liver preparation (solution of Liver Extract-Lilly, N. N. R.) after failure to respond to the daily parenteral administration of 2 cc. of the same preparation.

principle (other than that effective in pernicious anemia) was given when the material was administered orally than when it was injected. Thus, Case 3 received 5 cc. of the special liver preparation daily by intramuscular injection without effect, but thereafter received daily 51 cc.—10 times as much—of the same material by mouth with immediate and striking hematopoietic results (Fig. 3).

Case 4 was therefore studied in an attempt to ascertain whether the oral route of administration or the amount of the

unit (injectable) (Fig. 4). In a third period the patient received daily intravenous injections of 20 cc.—10 times as much—of the supernatant (98.5% by volume) of the special liver preparation and showed a prompt rise in reticulocytes to a peak of 25.1% on the 6th day. Since the only essential difference between the two therapeutic periods was the *amount* of liver extract given, it can be concluded that the response was due to the administration of a greater and thus adequate amount of some effective hematopoietic substance

other than the antipernicious anemia factor. Consequently, it appears that administration by the oral route is not necessary for effective response.

As indicated by the details of the report of Case 4, certain special features need discussion. The day preceding the reticulocyte peak in the third period the patient developed bronchopneumonia, but despite the presence of infection the reticulocyte response was striking. Since there was no evidence of infection in the first period, absence of response at that time cannot be attributed to this adverse factor. The liver extract was given intravenously in the third period rather than intramuscularly as in the first period because the daily intramuscular injection of 20 cc. of liver extract would have been too painful to be tolerated by the patient. No evidence exists of therapeutic failure in pernicious anemia because of lack of absorption of liver extracts given intramuscularly, and persistence of such an effect over several days is certainly unlikely in any patient.

An oral test made subsequently in Case 4 with 20 cc. daily of the same material that had previously been given intravenously (Fig. 4) resulted in a second reticulocyte rise to a peak of 7.4% on the 9th day. Such suggestive, though not conclusive, evidence of comparable potency of this preparation on oral administration presents a complete contrast to our experience in Addisonian pernicious anemia, in which its activity when orally administered has been found to be only about 1/60 of that when injected.⁴⁸ This observation suggests that the absorptive capacity of the alimentary tract in this patient was not significantly decreased, as it often is in patients with pernicious anemia, and constitutes evidence of an additional physiologic difference from pernicious anemia.

The chemical nature of the hematopoietic factor or factors effective in these patients is still obscure. Wills and Evans⁶¹ and Davis and Davidson²⁰ have hypothesized that both the principle effective in Addisonian pernicious anemia and an additional substance are required. An oppor-

tunity has not yet presented itself for determining whether the most refined liver extracts, if given in sufficient amounts, would still be ineffective and consequently would be judged as completely lacking in the additional substance. However, because in our hands Fraction G of Cohn, Minot and their associates¹⁵ in the form of the special liver preparation was active both orally and parenterally, it is not necessary to suppose that the special properties of the so-called "proteolyzed liver" of Davis and Davidson²⁰ are essential. This, of course, does not deny that relatively unrefined preparations of liver, including proteolyzed liver, may actually contain more of the unknown active principle than do more refined preparations. Moreover, it is not possible to be certain that the basic deficiency in the cases reported by Davis and Davidson is identical with that in each of the cases which we have described.

The fact that the diets of our patients were particularly deficient in animal protein does not imply that the dietary deficiency was necessarily due to protein itself, as Bethell^{3,4} has postulated for the macrocytic anemias of pregnancy. Indeed, the responses in Cases 3 and 4 following administration of a liver extract which is essentially free of protein¹⁵ clearly indicate that this effect could not have been due to protein as such. Nevertheless, requirement for a substance associated with animal protein, such as a member of the vitamin B complex, seems possible, as was suggested by Wills for her cases of tropical macrocytic anemia^{59,61} and for a similar experimentally produced nutritional macrocytic anemia in monkeys.⁶⁰ Very recently the ineffectiveness of additional identified components of the vitamin B complex as extrinsic factor or as "liver factor" in Addisonian pernicious anemia has been demonstrated.¹³ Case 4 likewise gave no response, during the second 10-day period, to the daily oral administration of large amounts of a mixture of the crystalline B vitamins and certain other accessory factors listed in the case sum-

mary, such as biotin, *L. casei* factor* and pyridoxal.^{41,43}

Reconsideration of observations on macrocytic anemias ascribed to deficiency of so-called food (extrinsic) factor. Reports have appeared in the literature of patients with macrocytic anemia who have exhibited hematopoietic responses to autolyzed yeast,^{12,56,58} dried yeast,^{22,62} beef muscle,^{12,33,47} or meat, eggs and milk.²⁷ Castle and his associates,⁹⁻¹² Groen and Snapper,²⁷ Kern,²⁸ Moore, Vilter, Minnich and Spies³³ and others have attributed such effects to an interaction between the food (extrinsic) factor in these various substances and effective amounts of gastric (intrinsic) factor co-existing with the hydrochloric acid usually present in the gastric contents of these patients. However, if such patients, like those in the present report, were actually incapable of response to usual doses of refined liver extract administered parenterally, the hematopoietic effects should not have been attributed to the oral administration of the food (extrinsic) factor, but rather to some other property of the materials. The 56 patients with macrocytic anemia associated with deficiency of the vitamin B complex, reported by Moore and his associates,³³ "showed prompt therapeutic response to the parenteral injection of highly purified liver extracts." Consequently, the responses to beef muscle, also demonstrated, may be considered as due to its content of extrinsic factor. As no tests with highly refined liver extracts were made in the cases of sprue studied by Castle, Rhoads, Lawson and Payne,¹² this causes some uncertainty with respect to their interpretation of the basis of effectiveness of beef muscle and milk and particularly of autolyzed yeast, which were hematopoietically active, respectively, in

8 and in 7 of 18 cases in which they were tried. However, unlike the patients in the present report, 8 of these 18 patients responded subsequently to 2 cc. amounts daily of parenterally administered liver extract (a solution of Liver Extract-Lilly, N. N. R.), as did 10 other patients. Except that the insoluble material had been removed, this liver extract was identical with that given as the special liver preparation without effect in 2 cc. and in 5 cc. amounts daily to Cases 4 and 3, respectively (see Figs. 4 and 3).

The interpretation of the observations of Strauss and Castle⁴⁵ on the etiology of the macrocytic anemias of pregnancy also needs critical re-examination. Case 5 of their report, as well as the first of the 2 additional cases synoptically described, demonstrates that normal human gastric juice was essential for the development of a significant hematopoietic response to the daily administration of 300 gm. of beef muscle or of 16 gm. of autolyzed yeast (Vegex), respectively. By contrast, in their Case 6 only insignificant reticulocyte responses occurred although beef muscle was given daily with hydrochloric acid and then, during 2 subsequent periods, with normal human gastric juice (Fig. 5). However, when 12.75 gm., or 1 U. S. P. unit (oral), of Liver Extract No. 343, N. N. R., (now called Liver Extract-Lilly, N. N. R.)³⁷ were given daily, a reticulocyte response of 46% and rapid hematologic and clinical improvement resulted. This observation suggests that the basic deficiency in Case 6 was not analogous to that in Addisonian pernicious anemia, but rather was like that in the cases reported in the present communication. If this is so, then 300 gm. of beef muscle, although containing adequate food (extrinsic) factor,^{9,11} are not a good source of the unknown active in-

* Subsequent to the submission of this manuscript for publication, both oral and parenteral administration of distinctly larger amounts of *L. casei* factor have been shown to be hematopoietically and clinically effective in nutritional macrocytic anemias, including Addisonian pernicious anemia, sprue and pernicious anemia of pregnancy. Whether patients similar to those reported here were included is not apparent from the published articles: DARBY, W. J., and JONES, E.: *Proc. Soc. Exp. Biol. and Med.*, 60, 259, 1945; MOORE, C. V., BIERBAUM, O. S., WELCH, A. D., and WRIGHT, L. D.: *J. Lab. and Clin. Med.*, 30, 1056, 1945; SPIES, T. D., VILTER, C. F., KOCH, M. B., and CALDWELL, M. H.: *South. Med. J.*, 38, 707, 1945; VILTER, C. F., SPIES, T. D., and KOCH, M. B.: *South. Med. J.*, 38, 781, 1945.

gradient present in Liver Extract-Lilly, N. N. R. It is thus probable that whenever, in the past, beef muscle has been administered orally with benefit in cases of macrocytic anemia,^{12,33,47} its activity has been due, as hitherto assumed, to its content of so-called food (extrinsic) factor. This conclusion is substantiated by the uniformity of response of their patients to beef muscle and gastric juice as well as to highly refined liver extract recently observed by Moore and his associates.³³ Thus, it is clear that within the group of

pernicious anemia when administered parenterally, produced no response. It therefore seems appropriate and convenient to designate the effective principle—which is as yet unidentified and which is apparently present in liver, proteolyzed liver, certain liver extracts and autolyzed yeast—as “Wills’ factor,” and to describe these particular macrocytic anemias as due to deficiency of that factor. Perhaps it would also be well to include under the term nutritional macrocytic anemia instances of macrocytic anemia due both to direct

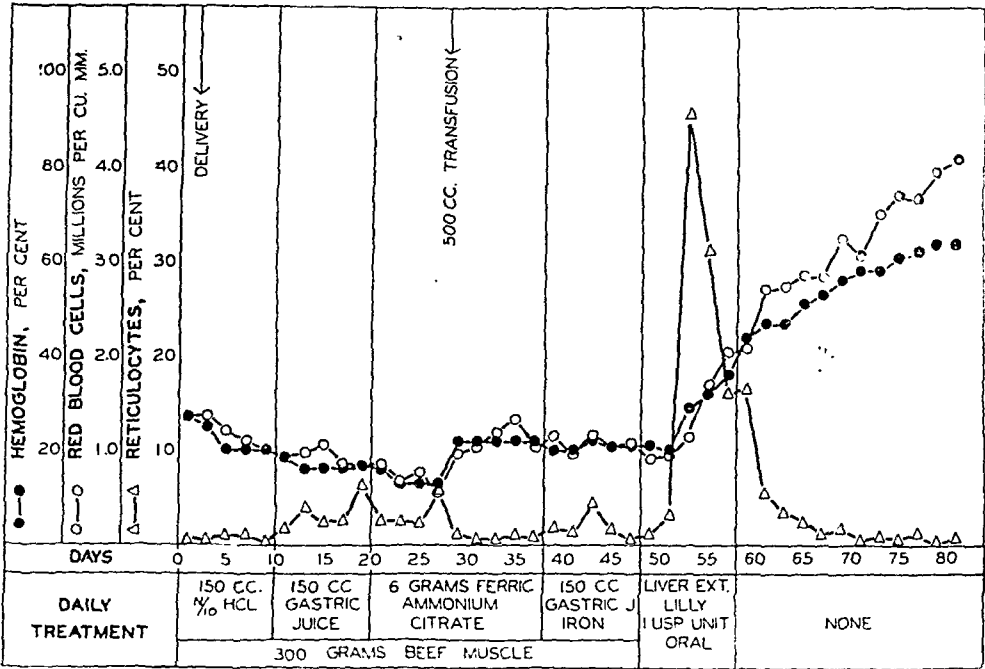


FIG. 5.—(Case 6 of Strauss and Castle.⁴⁷) Nutritional macrocytic anemia of pregnancy. Response to the oral administration of Liver Extract-Lilly, N. N. R., after failure to respond to the oral administration of beef muscle (extrinsic factor) and gastric juice (intrinsic factor).

cases of nutritional macrocytic anemia of pregnancy reported by Strauss and Castle, two therapeutically discrete varieties are now discernible.

Recognition and treatment of various types of nutritional macrocytic anemias. Dr. Lucy Wills deserves the credit for priority in demonstrating the effectiveness of autolyzed yeast in tropical macrocytic anemia of pregnancy⁵⁸ and for showing subsequently that in analogous anemias in monkeys,⁶⁰ certain refined liver extracts, although highly effective in Addisonian

and to conditioned nutritional deficiencies. This generic use of the term would include Addisonian pernicious anemia and the macrocytic anemias of pregnancy, sprue, fish tapeworm infestation, and so forth, as well as the anemias more obviously associated with dietary deficiencies presumably including Wills’ factor and the so-called extrinsic factor.

The clinical criteria for the selection of cases of nutritional macrocytic anemia due to deficiency of Wills’ factor have been summarized above. The clinical distinc-

tion from Addisonian pernicious anemia is clear. However, except by means of testing the response to refined liver extract, it remains to be seen whether a sharp distinction can be drawn between instances of deficiency of Wills' factor and instances of extrinsic factor deficiency. The expectation, considering the tendency to the development of multiple deficiencies in human malnutrition, is in favor of combinations of the two deficiencies.

It is possible that in addition to patients who respond to parenterally administered refined liver extracts, and to others who respond only to parenterally administered crude liver extracts, there is a third group who will respond only to still cruder, and thus necessarily orally administered, extracts of liver or to autolyzed yeast. The existence of this third group was suggested by Napier and his associates³⁶ and can be inferred from such reports as those of Trowell,⁵¹ Miller and Studdert,³¹ Fullerton,²⁵ Nielsen³⁸ and Davis and Davidson.^{19,20} Provisionally we have assumed that our 4 cases were alike in presenting the same nutritional deficiency. Case 4 responded to the special liver preparation when given intravenously in much larger amounts than could conveniently be given by intramuscular injection. Therefore the tentative conclusion can be drawn that the failure of the other 3 cases to respond to parenterally administered preparations was simply that these preparations, at least in the amounts given, did not contain enough Wills' factor to be effective. It is evident that the amount of Wills' factor does not parallel the U. S. P. unitage of these preparations, that is, their anti-anemic potency in Addisonian pernicious anemia. The fact that the principles effective in pernicious anemia and Wills' factor are apparently both present in certain liver extracts, and probably in varying proportions in different preparations, suggests an explanation of the conflicting experiences of others^{23,24,36,61} with parenterally administered refined liver extracts in tropical macrocytic anemias.

It may be of practical therapeutic im-

portance to keep in mind, in regard to patients with macrocytic anemia, that a failure to respond completely or partially to the parenteral administration of the usual dosage of a potent refined or crude liver extract should be followed by a trial of orally administered liver extract. For this purpose Liquid Extract of Liver, U. S. P.-Valentine and Liver Extract-Lilly, N. N. R., were found to be effective in the present observations, and no doubt similar products prepared by other pharmaceutical concerns would be equally so. If the patient is unable to tolerate oral medication, large amounts of an appropriate solution of Liver Extract-Lilly, N. N. R.,⁴⁸ given intravenously, as in Case 4, may be effective. It is possible, as is suggested by the experience of other investigators,^{18,20,25} as well as by our observations on Case 2, that oral preparations may be of value in the temperate zone not only in certain patients with macrocytic anemias of pregnancy but also in occasional patients among those usually classified as having "aplastic," "achrestic," "refractory," or "atypical pernicious" anemia. However, at least in this country, anemias due to deficiency of Wills' factor probably present rare exceptions to the principles which have been established with respect to the etiology and treatment of pernicious and related macrocytic anemias, particularly the clearly demonstrated advantage and convenience of parenterally administered refined liver extracts of known effectiveness in Addisonian pernicious anemia.

Case Reports. CASE 1. D. D., a 29 year old housewife, 7½ months pregnant, was admitted to the Second Medical Service of Boston City Hospital on September 13, 1943. Ten months before admission she had a sore throat, cold and cough lasting 3 months, associated with anorexia, malaise and loss of 40 pounds in weight. Six months before admission she developed increasing weakness, dizziness, easy fatigability and dyspnea on exertion. As a result of associated anorexia her diet had been very inadequate. In the last few weeks she had noticed slight

afternoon fever, night sweats, sore tongue and difficulty in swallowing. She had had no paresthesias at any time.

Past History. The patient had had 7 previous pregnancies resulting in 6 living children, the 4th of whom was hospitalized for the first 6 weeks of life because of jaundice. She had not been anemic during any of these pregnancies. In the year preceding her present illness she had had most of her teeth extracted, but had not obtained dentures.

Physical Examination. Temperature 99.2° F.; pulse 72; respirations 22; blood pressure 115/65. The patient was thin and pale. No icterus, purpura, or adenopathy was present. The tongue was dry and heavily coated, but showed no papillary atrophy. There was complete upper edentia and partial lower edentia, with some pyorrhea. The heart was normal except for a systolic murmur, heard best in the pulmonic area. There was abdominal enlargement consistent with a 7 to 8 months' pregnancy; the liver and spleen were not palpable. Vibratory sense was intact; reflexes were normal; there was no edema.

Laboratory Findings. The blood on admission showed: hemoglobin 26% (4.1 gm. %); red blood cells 1,420,000 per cmm.; hematocrit 13.0%; M. C. V. 91.5 μ .; M. C. H. C. 31.2%; M. C. H. 28.0 micro-micrograms; reticulocytes 0.4%; white blood cells 6400 per cmm., with a normal differential count. The stained smear showed slight anisocytosis, but no oval macrocytes, and a decrease in the number of platelets. The osmotic fragility of the erythrocytes was normal. The patient's blood was group O, Rh negative. Icterus index was 7½ units. Blood Hinton was negative. Blood non-protein nitrogen was 27 mg. %. The urine was negative except for Ehrlich's aldehyde reaction for urobilinogen, which was positive to a dilution of 1:128. Gastric analysis showed 1 cc. of N/10 free hydrochloric acid per 100 cc. of gastric juice in the fasting specimen and 2 cc. after histamine. The electrocardiogram was normal.

Course. The patient was considered to have pernicious anemia of pregnancy and was accordingly given intramuscularly, every other day over a period of 9 days, 1 cc. of Liver Injection, U. S. P.-Lederle* (Refined Solution Liver Extract Parenteral), contain-

ing 10 U. S. P. units (injectable) per cc. (Fig. 1). On the 4th day the patient was transfused with 400 cc. of whole blood. Because she showed no hematologic response, on the 7th and 8th days she was transfused with 450 cc. of whole blood and with the cells from 1100 cc. of blood, respectively. This brought the red blood cell count up to 3,500,000. During a second 10-day period the patient was given daily by intramuscular injection 2½ cc. of Liver Injection (Crude), U. S. P.-Wilson, containing 2 U. S. P. units (injectable) per cc. Again there was no increase in the reticulocytes or in the red blood cells. Beginning on the 20th day, for a third period of 17 days, the patient was given orally Liquid Extract of Liver, U. S. P.-Valentine,† 15 cc. 3 times daily, or 1 U. S. P. unit (oral). On the 6th day of this therapy the reticulocytes began to rise and reached a peak of 6.5% on the 13th day. On the 19th day the red blood cell count had reached 4,100,000. Coincident with the hematologic response there was marked improvement in the patient's appetite and in her general condition. Gastric analysis on the 13th day of therapy with orally administered liver extract showed an increase in acidity to 55 cc. of N/10 free hydrochloric acid per 100 cc. of gastric juice after histamine. On the 48th day after admission the patient gave birth to an Rh positive infant weighing 5 pounds and 6 ounces. This baby developed a mild hemolytic anemia of the newborn from which it recovered after several transfusions. The mother was discharged on November 17, 2 months after admission, in good health, and has remained so without further liver therapy. Blood studies 8 months after entry showed a hemoglobin of 94% and a red blood cell count of 4,760,000 per cmm. The platelets were abundant in the stained smear.

CASE 2. FIRST ADMISSION. A. M., a 35 year old housewife, was first seen on the Second Medical Service of the Boston City Hospital on August 5, 1942. In the 9 months before admission she had developed progressive fatigue, anorexia, pallor and dyspnea on exertion. Her dietary intake during this time had been relatively inadequate and as a result she had lost 50 pounds in weight. She had had one episode of sore tongue and mouth 3 months before admission. More re-

* Kindly supplied by Dr. Guy W. Clark of Lederle Laboratories, Inc.

† Kindly supplied by Mr. C. Braxton Valentine of Valentine's Meat-Juice Company.

cently she had had occasional vomiting, constipation, a burning sensation in her throat and a sense of numbness in her toes.

Physical Examination. Temperature 100° F.; pulse 120; respirations 35; and blood pressure 65/35. The patient was well nourished, but was very pale and appeared critically ill. Moderate dyspnea was present at rest. Both fundi showed numerous linear retinal hemorrhages. A small amount of pus was draining from the right auditory canal. The tongue was normal. The heart was slightly enlarged to the left, with a systolic murmur heard best in the pulmonic area. The liver was felt 3 finger-breadths below the costal margin, and was smooth, firm and non-tender. There was no splenomegaly, adenopathy, purpura, or icterus. Vibratory sense was normal; deep reflexes were active.

Laboratory Findings. Blood examination on admission showed: hemoglobin 12% (1.9 gm. %); red blood cells 500,000 per cmm.; hematocrit 5.1%; M. C. V. 102.0 μ .; M. C. H. C. 36.7%; M. C. H. 37.4 micro-micrograms; reticulocytes 0.6%; white blood cells 3400 per cmm., with a normal differential count. The stained smear showed moderate variation in size and shape of the erythrocytes, with polychromatophilia and Cabot rings but no oval macrocytes; multi-lobed neutrophils were common. The platelet count was 80,000 per cmm. The icterus index was 7 units. Blood non-protein nitrogen was 30 mg. %. The urine showed a maximum specific gravity of 1.023; initial specimens were loaded with white cells and contained albumin. Gastric analysis showed no free hydrochloric acid in the fasting specimen, but 10 cc. of N/10 free hydrochloric acid per 100 cc. of gastric juice were present after histamine.

Course. For the first 10 days the patient ran a fever ranging from 100° to 103° F., which was thought to be due to a urinary tract infection and which subsided on sulfadiazine therapy. During this first 10-day period the patient received one intramuscular injection of 5 cc. of Reticulogen-Lilly* and daily injections of 2 cc. of Liver Injection (Crude), U. S. P.-Armour,† containing 1 U. S. P. unit (injectable) per cc. There was no significant reticulocyte response during this time. However, 10 blood transfusions brought the red cell count to 3,010,000 per

cmm. The patient was discharged improved on August 28, 23 days after admission, with a final diagnosis of aplastic (refractory) anemia.

SECOND ADMISSION. Sixteen months later, on December 22, 1943, the patient was readmitted. Until 2 months before entry, she had been seen monthly in the Out Patient Department, where she received an intramuscular injection of 1 cc. of Liver Injection, U. S. P.-Lilly (Solution Liver Extract Purified), containing 15 U. S. P. units (injectable) per cc. On February 10, 1943 her red cell count was 4,790,000 per cmm., and on October 20 it was 3,200,000. About once in 3 months since discharge she had had mild epistaxes from her right nostril.

Physical Examination. Physical findings were essentially the same as on the previous admission except that the patient did not seem so ill and there were no retinal hemorrhages.

Course. On admission blood examination showed: hemoglobin 35% (5.5 gm. %); red blood cells 1,330,000 per cmm.; hematocrit 15.8%; M. C. V. 118.8 μ .; M. C. H. C. 34.6%; M. C. H. 41.0 micro-micrograms; reticulocytes 0.7%; white blood cells 4900 per cmm., with a normal differential count. During the 22 days of her hospital stay she received transfusions totaling 2000 cc. of whole blood and 1000 cc. of red cells from which the plasma had been removed. She was given no liver extract because she was thought to have aplastic anemia. On discharge on January 13, 1944, her hemoglobin was 91%, and she felt moderately improved.

THIRD ADMISSION. On March 20, 1944 the patient was readmitted. She had led a bed and chair existence in the 2 months intervening. From February 25 to March 1 she had been on a surgical service where she had a fistula-in-ano excised under spinal anesthesia. She had continued to have weakness, dyspnea, general asthenia and severe anorexia. She had experienced mild nosebleeds, but on the day before admission she had a severe one which was finally stopped after 6 hours by a nasal pack inserted by her physician.

Physical Examination. The patient had marked pallor. There was a nasal pack in the right nostril. A few small purpuric spots were present on her legs. Otherwise the find-

* Kindly supplied by Mr. George B. Walden, of The Lilly Research Laboratories.

† Kindly supplied by Dr. John H. Glynn of Armour Laboratories.

ings were unchanged from the previous admission.

Course. The patient had a fever rising as high as 103° F. for the first 5 days, during which time she continued to have severe epistaxes. Sulfapyrazine therapy resulted in subsidence of the fever and disappearance of pus cells from the urine. Blood examination on admission showed a hemoglobin of 27% (3.9 gm. %); red blood cells 1,450,000 per cmm.; hematocrit 12.0%; M. C. V. 89.0 μ .; M. C. H. C. 25.8%; M. C. H. 32.5 micrograms; reticulocytes 1.2%; white blood cells 3900 per cmm., with a normal differential count. The platelets were greatly diminished in the blood smear. The icterus index was 5 units.

The patient received 2500 cc. of blood in the first 5 days, which raised her red blood cells to 3,070,000 per cmm. Figure 2 shows only the last 2 transfusions of 500 cc. of whole blood. Then during a period of 10 days, from March 26 to April 4, she received daily intramuscular injections of 1 cc. of Reticulogen-Lilly and 2 cc. of Liver Injection (Crude), U. S. P.-Wilson, containing 2 U. S. P. units (injectable) per cc., without significant reticulocyte response (Fig. 2). This therapy was immediately followed in a second period by the oral administration of Liquid Extract of Liver, U. S. P.-Valentine, 15 cc. 3 times daily, or the equivalent of 1 U. S. P. unit (oral) daily. On the 4th day of this treatment the reticulocytes began to rise and reached a peak of 13% on the 6th day. Thereafter the patient made rapid and dramatic clinical improvement, and her appetite and sense of well-being increased markedly. Epistaxes, which had previously been frequent, severe and difficult to control, subsided. The patient was discharged on April 15, 4 weeks after admission.

Since discharge the patient has been seen regularly at frequent intervals. She continued taking Liquid Extract of Liver, U. S. P.-Valentine until May 24, 2 months after entry, at which time blood examination showed a hemoglobin of 93%, red cells 4,140,000 per cmm., and white cells 8200 per cmm. The patient stated that she felt the best that she had ever felt and that she had an insatiable appetite. She had had no nosebleeds for a month and no purpura. The liver was no longer palpable.

CASE 3.* M. B., a 40 year old primipara at term, was admitted to the Obstetrical Service of the Boston City Hospital in labor on May 24, 1944. She had been in good health until about 3 months before admission, when her appetite, always somewhat poor, began to diminish noticeably. Anorexia increased progressively so that during the last 3 weeks she subsisted entirely on occasional egg-nogs. Two and one-half months before admission she developed increasing ankle edema, fatigability and pallor. Heartburn became distressing and on several occasions was associated with vomiting. Four weeks before entry her tongue became increasingly sore, especially at the margins. During the last week she had occasional mild nosebleeds and a few purpuric spots on her body. She had no paresthesias and no diarrhea at any time. She had never been anemic.

Physical Examination. Temperature 100° F.; pulse 120; respirations 20; blood pressure 120/80. The patient was a thin woman with waxen pallor, in active labor, appearing critically ill. There were 15 to 20 purpuric spots, averaging about 0.5 cm. in diameter, on the trunk and extremities. No icterus or adenopathy was present. The tongue was slightly reddened at the margins, but showed no papillary atrophy. There was a small ulceration on the left tonsillar pillar. The heart was normal except for a systolic murmur, heard best at the apex. The abdomen contained a protuberant mass consistent with a full term pregnancy. The liver and spleen were not palpable. There was obvious pitting edema of the ankles. Vibratory sense was intact; reflexes were normal.

Laboratory Findings. The blood examination on May 25 revealed: hemoglobin 37% (5.8 gm. %); red blood cells 1,720,000 per cmm.; hematocrit 15.8%; M. C. V. 91.8 μ .; M. C. H. C. 27.3%; M. C. H. 33.5 micrograms; reticulocytes 0.6%; white blood cells 3500 per cmm., with a normal differential count. The stained smear showed little variation in size and shape of the erythrocytes, with rare round but no oval macrocytes. Platelets were sparse and large. The neutrophils had toxic granules. The platelet count was 57,000 per cmm. The blood group was B, Rh positive. Icterus index was 4 units. The urine had a specific gravity of 1.020 and contained 1 plus albumin; the

* This patient was seen in consultation with Dr. C. D. Smith by Dr. Peter F. Weiss, who referred her to the Boston City Hospital. We are indebted to Dr. Weiss and to the Obstetrical Service of the Hospital for permitting us to study the patient.

sediment showed a few white blood cells, red blood cells and casts. Urine urobilinogen was positive to a dilution of 1:4. Gastric analysis on June 1 showed no free hydrochloric acid in the 3 cc. of fasting specimen, but after histamine there were 45 cc. of N/10 free hydrochloric acid per 100 cc. of gastric juice.

Course. On May 25, the day after admission, the patient was delivered by low forceps, under spinal anesthesia, of a normal female infant weighing 4 pounds and 2 ounces. Uterine bleeding was not excessive. During a period of 8 days the patient was given daily intramuscular injections of 5 cc. of a "special liver preparation" (Fig. 3). This material was a suspension-solution of Liver Extract-Lilly, N. N. R.,* containing 1.25 gm. per 5 cc., equivalent to about 2.5 U. S. P. units (injectable). During this course of therapy there was some decline in the red blood cell count, and the patient continued to appear gravely ill. From the 2nd to the 23d day she ran a fever ranging from 101° to 103° F. Although there was no specific evidence for a source of infection, sulfadiazine was given from the 4th to the 16th day but produced no appreciable clinical response. The pulse rate remained at 120. On June 2, 8 days after delivery, the patient's condition appeared so serious that parenteral liver extract therapy was abandoned. During a second period she was then given by mouth the same preparation that she had been given parenterally, receiving daily, in 3 doses, 51 cc., containing 12.75 gm. of Liver Extract-Lilly, N. N. R., or the equivalent of 1 U. S. P. unit (oral). Within 3 days after initiation of this therapy clinical improvement was noted coincidentally with a rise in reticulocytes, which reached a peak of 26.2% on the 7th day. This response was accompanied by a sustained rise in hemoglobin and red blood cell values. The patient's appetite improved strikingly and her edema disappeared. On June 16 the blood platelets had risen to 372,000 per cmm. The patient was discharged remarkably improved on June 21, 29 days after admission. Liver extract therapy was discontinued 1 month after discharge, since the hemoglobin had reached 84% and the red blood cell count was 4,100,000 per cmm. Following discharge the patient's brown hair fell out, and was replaced by a new growth of white hair. On

February 20, 1945, 8 months after discharge, the blood count was still normal.

CASE 4. S. G., a 76 year old housewife, was admitted to the Second Medical Service of Boston City Hospital on January 2, 1945. For 2 years the patient's appetite had diminished progressively so that her dietary intake for some time had consisted largely of oatmeal, tea and toast. She had never cared for meat and seldom ate it. For 4 weeks before admission she had had increasing fatigue, pallor and frequent vomiting. She gave no history of glossitis, neural symptoms, fever, jaundice or blood loss.

Physical Examination. Temperature 101° F.; pulse 120; respirations 22; blood pressure 110/45. The patient was a very pale, thin, white-haired elderly lady. No jaundice, purpura, or adenopathy was present. There were a few small punctate retinal hemorrhages in the right fundus. The tongue appeared normal. There was complete edentia. A few scattered moist râles were heard at both lung bases. The heart was normal except for a soft blowing systolic murmur of maximum intensity at the apex. The liver and spleen were not palpable. Neurologic examination was negative. There was no peripheral edema.

Laboratory Findings. The blood on admission showed: hemoglobin 25% (3.9 gm. %); red blood cells 1,230,000 per cmm.; hematocrit 13.8%; M. C. V. 112.2 cμ.; M. C. H. C. 28.3%; M. C. H. 31.7 micro-micrograms; reticulocytes 2.6%; white blood cells 2800 per cmm. (76% segmented neutrophils, 10% band forms, 6% small lymphocytes, 1% large lymphocytes, and 7% monocytes). The stained smear showed moderate anisocytosis and poikilocytosis, with oval macrocytes and a few nucleated red cells and Howell-Jolly bodies. The platelet count was 98,000 per cmm. The icterus index was 7½ units. The patient's blood was group A, Rh positive. Blood non-protein nitrogen was 29 mg. %. Plasma albumin was 2.39 gm. %, globulin 2.14%, with a total protein of 4.53 gm. %. Blood Hinton test was negative. The urine showed a trace of albumin and a positive reaction for urobilinogen in a dilution of 1:32. Stools were guaiac negative. Gastric analysis showed 17 cc. of N/10 free hydrochloric acid per 100 cc. of gastric juice in the 25 cc. of fasting specimen, and 18 cc. after histamine.

* Kindly supplied by Mr. George B. Walden of The Lilly Research Laboratories.

Stool urobilinogen excretion studies showed the following values: 43.75 mg. per day for the 4-day period immediately preceding intravenous liver extract therapy (16th to 20th day), 182.7 mg. per day for the succeeding 4-day period (20th to 24th day), and 15 mg. per day for the 4-day period from the 36th to the 40th day.

Course. The patient's temperature gradually subsided and became normal on the 4th day after admission. She received ferrous sulphate, 4 grains 3 times daily, throughout her hospital stay. During a first 10-day period she was given daily, by intramuscular injection, 2 cc. of a suspension-solution of Liver Extract-Lilly, N. N. R., equivalent to about 1 U. S. P. unit (injectable). She showed no hematologic response to this therapy (Fig. 4). She was given a total of 900 cc. of whole blood during the last 3 days of this period and this raised her red blood cell count to 1,880,000 per cmm. During a second 10-day period she received daily, by mouth, crystalline B vitamins and accessory substances in the following amounts: thiamine chloride, 100 mg.; riboflavin, 100 mg.; niacinamide, 200 mg.; pyridoxine hydrochloride, 100 mg.; pyridoxal hydrochloride, 300 mg.; calcium pantothenate, 100 mg.; paraminobenzoic acid, 2 gm.; choline hydrochloride, 300 mg.; inositol, 200 mg.; biotin, 2 mg.; and *L. casei* factor, 1.3 mg.* These were mixed with 10 gm. of Borden's "Labco vitamin-free casein" and administered in 60 cc. of water. Again the patient failed to show any hematologic improvement. She was then started on a third period of therapy, receiving daily intravenous injections of 20 cc. of the supernatant from the suspension-solution of Liver Extract-Lilly, N. N. R., which was derived from 5 gm. of the powder and was equivalent in antianemic potency to about 10 U. S. P. units (injectable). The supernatant resulted from removal of 1.5% by volume of precipitate contained in the suspension-solution. This preparation was given in 250 cc. of 5% glucose in distilled water at the rate of 5 cc. per minute, in order to avoid causing flushing and dyspnea. On the 4th day of this therapy the reticulocytes began to rise and reached a maximum of 25.1% on the 6th day. Therapy was then discontinued because of the excellent hemat-

ologic response and because of the patient's dislike of venepunctures. On the day preceding the reticulocyte peak the patient developed clinical signs of bronchopneumonia. This diagnosis was confirmed by Roentgen ray and sulfadiazine was given for 2 days but produced no improvement. Penicillin was then given for 3 days. The patient improved clinically within 24 hours and remained afebrile thereafter. On February 2, 5 days after discontinuance of intravenous liver extract therapy, daily oral administration of 20 cc., the same amount, of the same preparation was begun. On the 3d day the patient's appetite began to improve noticeably and thereafter clinical improvement was rapid. There was a second rise of reticulocytes beginning on the 6th day and reaching a peak of 7.4% on the 9th day. This was accompanied by a rise in red blood cells to 3,480,000 per cmm. on February 27, 3 days before discharge on the 57th day of hospitalization. One month later the red blood cells had risen to 4,320,000 per cmm.

Conclusions. 1. Three cases of nutritional macrocytic anemia, 2 of which occurred during pregnancy, were shown under controlled clinical conditions to respond to orally administered liver extract immediately after failing to respond to multiple U. S. P. units (injectable) of parenterally administered liver extract. A fourth case responded immediately to parenterally administered liver extract when the dose was increased 10 fold.

2. As a result of a review of the literature, as well as of the observations on these 4 patients, it is apparent that at least two, and possibly three, types of nutritional deficiency are involved in nutritional macrocytic anemias, as evidenced by differences in therapeutic responses to various types of liver extracts:

a. Response to usual amounts of the most refined liver extracts administered parenterally. This is a large group, including Addisonian pernicious anemia and many cases of sprue and macrocytic anemia of pregnancy.

* "Folic acid" concentrate (*L. casei* factor 15% pure, prepared by fermentation methods) was obtained through the courtesy of Dr. Y. Subbarow, Lederle Laboratories, Inc.; other vitamins were obtained through the courtesy of Dr. D. F. Robertson, Merck & Co., Inc.

b. Response *only* to orally administered crude liver extracts or to large amounts of certain relatively crude liver extracts given parenterally. This group includes certain instances of macrocytic anemia of the tropics, of anemia of pregnancy and of "refractory" anemias with megaloblastic bone marrow, as well as the cases presented here.

c. As to a third type, it is possible that the basic deficiency in our 2 patients who responded to orally administered crude liver extract differs from that in the 2 patients who responded to large amounts of more refined liver extract.

3. Since a distinction in therapeutic response to refined and crude liver extracts was first reported in anemic monkeys, and later in patients, by Dr. Lucy Wills and her associates, it is suggested that this effective principle in crude liver extracts and in autolyzed yeast be designated as "Wills' factor." It clearly differs from the principle in liver which is effective in Addisonian pernicious anemia and from the so-called extrinsic factor.

4. Observations on Case 4 indicated that Wills' factor is not identical with various pure components of the vitamin B complex and accessory nutritional substances, including biotin, *L. casei* factor and pyridoxal.

5. In instances of macrocytic anemia refractory to parenterally administered liver extract, especially those associated with pregnancy, it may be of practical therapeutic importance to test the efficacy of relatively crude liver extracts administered orally or, when suitably prepared, administered intravenously in large amounts.

6. The demonstrated therapeutic value of orally administered liver extracts in occasional patients with nutritional macrocytic anemia due to deficiency of Wills' factor should not obscure the well-established advantages of parenterally administered refined liver extracts in the treatment of the majority of patients with nutritional macrocytic anemias, especially those with Addisonian pernicious anemia.

We are greatly indebted to the following: Miss Marion C. Shorley for editorial assistance; Miss Geneva A. Daland and Miss Ruth E. Pearson for performing the blood examinations; Miss Cynthia Barker and Miss Theo Wood for preparation of the charts; and Mr. Theodore Kisil for fecal urobilinogen studies.

REFERENCES

1. ABRAMSON, L.: *Acta med. Scandinav.*, **96**, 319, 1938.
2. BARKER, W. H., and HUMMEL, L. E.: *Bull. Johns Hopkins Hosp.*, **64**, 215, 1939.
3. BETHELL, F. H.: *J. Am. Med. Assn.*, **107**, 364, 1936.
4. BETHELL, F. H., BLECHA, E., and VAN SANT, J. H.: *J. Am. Diet. Assn.*, **19**, 165, 1943.
5. BOMFORD, R. R., and RHOADS, C. P.: *Quart. J. Med.*, **10**, 175, 1941.
6. VON BONSDORFF, B.: *Acta med. Scandinav.*, **105**, 516, 1940.
7. CALLENDER, S. T. E.: *Quart. J. Med.*, **13**, 75, 1944.
8. CASTLE, W. B.: *AM. J. MED. SCI.*, **178**, 748, 1929.
9. CASTLE, W. B.: *Science*, **82**, 159, 1935.
10. CASTLE, W. B.: *Trans. Coll. Phys. Philadelphia*, **7**, 129, 1939.
11. CASTLE, W. B., and HAM, T. H.: *J. Am. Med. Assn.*, **107**, 1456, 1936.
12. CASTLE, W. B., RHOADS, C. P., LAWSON, H. A., and PAYNE, G. C.: *Arch. Int. Med.*, **56**, 627, 1935.
13. CASTLE, W. B., ROSS, J. B., DAVIDSON, C. S., BURCHENAL, J. H., FOX, H. J., and HAM, T. H.: *Science*, **100**, 81, 1944.
14. CASTLE, W. B., TOWNSEND, W. C., and HEATH, C. W.: *AM. J. MED. SCI.*, **180**, 305, 1930.
15. COHN, E. J., MINOT, G. R., ALLES, G. A., and SALTER, W. T.: *J. Biol. Chem.*, **77**, 325, 1928.
16. DAKIN, H. D., and WEST, R.: *J. Biol. Chem.*, **109**, 489, 1935.
17. DAVIDSON, L. S. P., DAVIS, L. J., and INNES, J.: *Brit. Med. J.*, **2**, 31, 1942.
18. DAVIDSON, L. S. P., DAVIS, L. J., and INNES, J.: *Edinburgh Med. J.*, **50**, 431, 1943.
19. DAVIS, L. J.: *Arch. Dis. Child.*, **19**, 147, 1944.
20. DAVIS, L. J., and DAVIDSON, L. S. P.: *Quart. J. Med.*, **13**, 53, 1944.
21. ELLIOTT, G. A.: *J. Obst. and Gynec. Brit. Emp.*, **51**, 198, 1944.
22. ELSON, K. O., and SAMPLE, A. B.: *J. Clin. Invest.*, **16**, 463, 1937.
23. FAIRLEY, N. H.: *Lancet*, **1**, 1118, 1940.
24. FOY, H., and KONDI, A.: *Lancet*, **2**, 360, 1939.
25. FULLERTON, H. W.: *Brit. Med. J.*, **1**, 158, 1943.
26. GÄNSLEN, M.: *Klin. Wchnschr.*, **9**, 2099, 1930.
27. GROEN, J., and SNAPPER, I.: *AM. J. MED. SCI.*, **193**, 633, 1937.
28. KERN, R. A.: *Ann. Int. Med.*, **5**, 729, 1931-32.
29. LESCHER, F. G.: *Lancet*, **2**, 148, 1942.

30. MILLER, D. K., and BARKER, W. H.: *Arch. Int. Med.*, **60**, 385, 1937.
31. MILLER, H. G., and STUDDERT, T. C.: *Lancet*, **2**, 332, 1942.
32. MINOT, G. R., and CASTLE, W. B.: *Lancet*, **2**, 319, 1935.
33. MOORE, C. V., VILTER, R., MINNICH, V., and SPIES, T. D.: *J. Lab. and Clin. Med.*, **29**, 1226, 1944.
34. MUDALIAR, A. L., and MENNON, M. K.: *J. Obst. and Gynec. Brit. Emp.*, **49**, 284, 1942.
35. NAPIER, L. E.: *Indian Med. Gaz.*, **74**, 1, 1939.
36. NAPIER, L. E., DAS GUPTA, C. R., CHAUDHURI, R. N., SEN, G. N., RAI CHAUDHURI, M. N., SEN GUPTA, P. C., and MAJUMDER, D. N.: *Indian Med. Gaz.*, **73**, 385, 1938.
37. *New and Nonofficial Remedies*, 1941.
38. NIELSEN, O. P.: *Acta med. Scandinav.*, **108**, 421, 1941.
39. PORTER, W. B., WILLIAMS, J. P., FORBES, J. C., and IRVING, H.: *J. Am. Med. Assn.*, **93**, 176, 1929.
40. RODRIGUEZ-MOLINA, R.: *Puerto Rico J. Pub. Health and Trop. Med.*, **15**, 177, 1939.
41. SCOTT, M. L., NORRIS, L. C., HEUSER, G. F., and BRUCE, W. F.: *J. Biol. Chem.*, **158**, 291, 1945.
42. SEGERDAHL, E.: *Acta med. Scandinav.*, **108**, 483, 1941.
43. SNELL, E. E.: *J. Biol. Chem.*, **154**, 313, 1944.
44. STEVENSON, E. M. K.: *Obst. Trans. Edinburgh*, **97**, 81, 1938.
45. STRAUSS, M. B., and CASTLE, W. B.: *New England J. Med.*, **207**, 55, 1932.
46. STRAUSS, M. B., and CASTLE, W. B.: *J. Am. Med. Assn.*, **98**, 1620, 1932.
47. STRAUSS, M. B., and CASTLE, W. B.: *AM. J. MED. SCI.*, **185**, 539, 1933.
48. STRAUSS, M. B., TAYLOR, F. H. L., and CASTLE, W. B.: *J. Am. Med. Assn.*, **97**, 313, 1931.
49. STURGIS, C. C., and GOLDHAMER, S. M.: *Ann. Int. Med.*, **12**, 1245, 1938-39.
50. SUAREZ, R. M.: *Ann. Int. Med.*, **12**, 529, 1938-39.
51. TROWELL, H. C.: *Lancet*, **1**, 43, 1943.
52. UNGLEY, C. C.: *Lancet*, **1**, 925, 1938.
53. UNGLEY, C. C., DAVIDSON, L. S. P., and WAYNE, E. J.: *Lancet*, **1**, 349, 1936.
54. *U. S. Pharmacopœia XII*, 1942.
55. *U. S. Pharmacopœia XII*, First Bound Suppl., p. 36, 1943.
56. VAUGHAN, J. M., and HUNTER, D.: *Lancet*, **1**, 829, 1932.
57. WATSON, J., and CASTLE, W. B.: *Proc. Soc. Exp. Biol. and Med.*, **58**, 84, 1945.
58. WILLS, L.: *Brit. Med. J.*, **1**, 1059, 1931.
59. WILLS, L.: *Indian J. Med. Res.*, **21**, 669, 1934.
60. WILLS, L., CLUTTERBUCK, P. W., and EVANS, B. D. F.: *Biochem. J.*, **31**, 2136, 1937.
61. WILLS, L., and EVANS, B. D. F.: *Lancet*, **2**, 416, 1938.
62. WINTROBE, M. M.: *AM. J. MED. SCI.*, **197**, 286, 1939.

HOOKWORM INFECTION IN AMERICAN TROOPS IN ASSAM AND BURMA

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A CLINICAL picture characterized by the acute onset of moderately severe gastro-intestinal symptoms associated with eosinophilic leukocytosis and hookworm infection was observed with increasing frequency in this hospital. It occurred predominantly in combat troops serving in North Burma during the summer and fall of 1944. It differed from the traditional clinical picture of hookworm disease chiefly in the abruptness of onset, the prominence of acute and sometimes disabling digestive symptoms and the lack of anemia. It presented problems of management, diagnosis and treatment of sufficient importance to prompt this report of 50 cases. These cases represent 50 consecutive instances of hookworm infection admitted or transferred to the gastro-intestinal and dysentery wards, and are therefore a selected group. Several hundred additional cases both with and without symptoms were seen on the general medical wards during the same period of time.

Clinical Features. Gastro-intestinal symptoms were predominant and were the primary reason for admission in well over half of these patients. In others who had been admitted for wounds or malaria, abdominal complaints became prominent during convalescence. In 7 of the group, abdominal symptoms had subsided by the time the diagnosis was made. The digestive symptoms began a few weeks to several months after the men arrived in North Burma. In many, a sudden onset of nausea, vomiting, abdominal pain and diarrhea occurred. In others, a more gradual onset of cramping and burning

abdominal pains after meals were the initial manifestations. The nausea, vomiting and diarrhea tended to subside and to become intermittent.

Pain was the most prominent and persistent of the gastro-intestinal symptoms. Its location was usually epigastric but sometimes was periumbilical or in either the left or right upper quadrants. In general it was not localized to a single area but tended to be diffuse. The pain was variously described as burning, cramping, or aching. Its most definitive characteristic was its appearance immediately after meals. It was not relieved by eating. Certain foods, particularly fried greasy food and beer frequently made the pain worse. In a few instances, the epigastric pain somewhat resembled that of a peptic ulcer, coming intermittently and sometimes awakening the patient at night. The diffuseness of the pain, its usual occurrence immediately after meals, and the association with diarrhea were the clinical characteristics which aided in differentiating hookworm infestation from peptic ulcer. Results of gastro-intestinal Roentgen rays and stool examinations were the final criteria.

Diarrhea was a prominent and sometimes intractable symptom. The number of stools per 24 hours averaged about 6. Unless complicated by amebiasis, no blood, pus, or mucus were noted in the feces. The diarrhea was never associated with urgency or tenesmus. Amebiasis was always considered, but the prominence of upper abdominal symptoms, together with the absence of rectal symptoms and dysenteric

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stools with exudate, frequently enabled a differentiation to be made on a clinical basis.

The patients commonly maintained that they had developed "stomach trouble" from the C and K rations provided in the forward areas. However, when a hospital diet was provided their symptoms did not improve, and the anorexia, blamed on the unpalatable rations, persisted. This was in marked contrast to the healthy and vigorous appetites of other convalescent patients who did not have hookworm disease.

usually common. The cough often persisted from a week to several months after the last suspected exposure to hookworm larvæ.

The physical findings were not striking except for the almost universal loss of from 10 to 40 pounds in weight. In a few cases the weight loss was great enough to make the patients appear emaciated. It is true that weight loss among the combat soldiers in Burma was a common occurrence because of difficulties in obtaining palatable food, but the inability of the patients with hookworm disease to gain

TABLE 1.—SYMPTOMS OF HOOKWORM INFECTION

	No. of cases in which a reliable history could be obtained	No. positive	% positive
Abdominal pain	49	42	86
Weight loss	36	29	80
Respiratory symptoms	41	29	70
Abdominal tenderness	48	32	66
Vomiting	46	27	58
Diarrhea	48	25	52
History of ground itch	42	12	28

The history of a skin rash which might be considered to be a "ground itch," caused by migration of the larvæ through the skin, was never volunteered. However, when the diagnosis of hookworm had been established and the patients specifically questioned on this point, about one quarter of them gave a suggestive history. The evaluation of this history was difficult because the incidence of other skin lesions among combat troops was high; miliaria, leech bites, and fungus infections were common, but some patients recalled having had intensely itching eruptions on the legs and thighs after sleeping in foxholes.

Respiratory symptoms which might be attributed to the passage of hookworm larvæ through the lungs were elicited in 70% of the patients. Many described a so-called "foxhole cough," well remembered because at night it gave away the soldier's position to the enemy. Again, the importance of this history has to be qualified. Upper respiratory infections were undoubtedly frequent, but the complaint of a "deep chest cold" without any preceding coryza or sore throat was un-

weight frequently persisted even after hospitalization when the diet was much improved in quantity and palatibility. A low grade fever of 99° to 100° F. which could not otherwise be explained, was present in a small number of hookworm patients. Upper abdominal tenderness was found in slightly more than half. Usually more than one tender area was found. In some patients, right upper quadrant tenderness was quite marked, and when in addition the liver edge was palpable, amebic hepatitis had to be excluded. Hyperactive peristalsis was frequently present. Three patients had bouts of otherwise unexplained urticaria while under observation.

One patient was admitted who gave such a straightforward and illuminating story about the development of his symptoms that the history is given in detail since the time relationship of the described symptoms is of interest in relation to the known life cycle of the parasite.

Case Abstract. A 25 year old white sergeant from an engineering unit was admitted

to this hospital on Nov. 27, 1944. His chief complaint was diarrhea of 2 weeks duration. This consisted of 6 to 8 watery stools a day without any blood or mucus. It was associated with abdominal pain which had never been violent or attended by urgency or tenesmus. In addition to the diarrhea he complained of burning upper abdominal pain, vomiting, and anorexia. These symptoms suggested hookworm infection. With this in mind the patient was questioned about rash and cough. He then gave this history: On Oct. 27, 1944, a month prior to admission he crawled under a mobile truck-crane and worked with his back on the ground for more than an hour. His shirt tails were outside of his trousers thereby exposing his skin directly to the ground. In addition he had a large hole in his shirt which exposed to the ground an area of skin between his scapulæ. He experienced sensations which he interpreted as being due to having straw in his shirt. He removed his shirt and shook it out. This did not relieve the itch. He was so disturbed that night that he reported to his dispensary. The medical technician told him that he had a rash resembling poison ivy. The itching eruption continued for another 2 days and then subsided. During the night of Oct. 30, 1944, the fourth day after working under the truck, the patient was awakened with a deep cough. He volunteered that the symptoms were different from an ordinary chest cold and this made him fear that he might be getting pneumonia. He again reported to sick call and was told that he had bronchitis. The cough persisted for 12 days. At noon on Nov. 12, 1944, 14 days after exposure the patient, having eaten lunch, suddenly felt bloated and began to vomit. From then on he had burning, cramping abdominal pain which was made worse by eating. He vomited frequently. On Nov. 16, 1944 diarrhea began. His gastrointestinal symptoms did not respond to the usual dispensary remedies and he was referred to this hospital for further studies. Examination revealed an unhappy and haggard, but well developed and nourished soldier. Abdominal palpation disclosed a diffuse mild upper abdominal tenderness and two fairly localized areas of more marked tenderness, one in the left upper quadrant and the other in the left lower quadrant of the abdomen. No rash or signs of pulmonary disease were present. A clinical diagnosis of hookworm

disease was made. On the following day examination of a direct saline suspension of stool revealed hookworm eggs. Blood studies revealed 16.2 gm. of hemoglobin and a total leukocyte count of 13,100 (neutrophils 11%, lymphocytes 21%, monocytes 2%, and eosinophiles 66%). Gastro-intestinal Roentgen ray studies were reported by Captain George P. Keefer to show a small intestinal pattern characteristic of hookworm disease.³ The chest Roentgen ray was negative. The patient was given 3 cc. of tetrachlorethylene and his stools were collected for the next 24 hours. A total of 64 adult hookworms was recovered: 43 were *Ancylostoma duodenale* and 21 were *Necator americanus*. A week later the patient was symptomatically much improved. A few eggs were seen in a concentrated specimen though none was found on direct examination. The leukocyte count had dropped to 8000 of which only 30% were eosinophiles. One gm. of hexylresorcinol was then administered. At the end of another week a few eggs were still found in the feces by the concentration technique. The leukocyte count was then 6400 with 25% eosinophiles and the patient had become symptom free. He was then given a third vermifuge consisting of 3 cc. of tetrachlorethylene. Four and 10 days later concentrated specimens were negative for hookworm eggs. The blood count revealed 6200 leukocytes with 54% polymorphonuclear leukocytes, 40% lymphocytes, and 6% eosinophiles. The patient was discharged to duty on Jan. 12, 1945, completely recovered.

This patient's history gave a remarkably clear picture of the time relationships between the entrance of the larvæ into the skin and the appearance of the symptoms resulting from the migration of the parasite through the lungs to the small intestines. In a number of other patients a similar clearcut sequence of symptoms could be uncovered by detailed questioning. In most instances where the duration of exposure extended over a period of weeks, the patients could remember when their gastro-intestinal symptoms began but the date of onset of itching skin eruption and cough could not be recalled.

Laboratory Studies. The definite diagnosis of hookworm infection depended

upon the demonstration of the eggs in the stool. For this purpose the direct examination, even when repeated several times, was not a satisfactory procedure. It was only after the zinc sulfate flotation centrifugation technique² was adopted, that the eggs could be found consistently. This difference between the two methods is amply demonstrated by the following results.

Of the 50 patients considered in this report, the stools of 42 were first examined by the direct method. The diagnosis was established after repeated examinations in only 24 (57%) of the patients. Only 9 (21%) had positive stools on the initial examination. On the other hand 35 of the patients had stools examined by the concentration method. In all 35, hookworm eggs were found after not more than 3 stool examinations and in 30 (86%) they were demonstrated on the initial examination. A positive report was obtained from the laboratory on the first trial in 8 of 10 patients in whom the direct method had failed from 5 to 10 times. In all, of 145 stools examined by the direct method only 24 (17%) were positive whereas of 46 stools examined by the concentration technique 38 (82%) were positive for hookworm eggs.

Charcot-Leyden crystals in the stools are regarded as an abnormal finding which may be indicative of intestinal parasitism. Where specifically looked for, these crystals were found in the stools of 18 of 27 patients.

In 14 of the patients, 24-hour stools were collected following vermifuge and examined for adult hookworms. In specimens from 13 patients, the number of adults recovered by detailed, systematic study averaged 37. In a specimen from the remaining patient, over 100 adults were identified. On the basis of these examinations and those for eggs, the worm burden was considered small. No egg counts were performed, but the number of eggs encountered by the direct and concentration methods of examination was considered further evidence for assuming a small worm burden. *A. duodenale* was

identified in 12 of the 14 specimens studied in this manner. Two of these in addition had *N. americanus*, and the remaining 2 had *N. americanus* only.

Among the striking features observed, was the degree of eosinophilia. Its discovery was the chief reason for the examination of the stool for eggs in many instances. The maximum eosinophilia recorded was 70%, with a total leukocyte count of 41,000. The more usual finding was an eosinophilia of 40% with about 15,000 leukocytes. Fluctuation in both the total leukocyte count and the percentage of eosinophiles was very common. The earliest time for appearance of eosinophilia after the suspected date of infection in these 50 patients was 30 days. The eosinophilia persisted in most of them to a diminished degree for weeks and months despite frequent vermifuges.

Anemia was neither marked nor constant, a hemoglobin of 12 gm. or below being present in but 6 patients in this group. A severe wound, falciparum malaria or scrub typhus were at least partly responsible for the anemia in 3 of these 6.

Gastro-intestinal Roentgen ray studies were made in 42 of these patients.³ In 34, abnormalities of the small intestinal pattern were noted. These varied from mild rugal thickening and increased tone to a very marked change in the appearance of the bowel. Tenderness was elicited over involved bowel loops. The abnormalities were most prominent in the jejunum but the distal duodenum was also involved. In 14, the roentgenologist was able to make a presumptive diagnosis of hookworm infestation. In 4 patients the deep broad indentations in the column of the barium made by the thickened rugal folds of the jejunum were very striking. Captain George P. Keefer suggested the term "cogwheel" pattern which describes its appearance very well. Mild degrees of this type of gastro-intestinal Roentgen ray change were reported in patients in whom hookworm infection was not demonstrated. However, when the alterations were marked, errors were infrequent. Some-

times the roentgenologist correctly suggested the diagnosis before it had been suspected on clinical grounds. The roentgenologic manifestations were remarkably persistent. In some they outlasted the symptoms.

Epidemiology and Incidence. Most of these patients were combat soldiers. The remainder were service troops living under field conditions. These men had served in areas lacking adequate sanitation, sleeping in foxholes partially filled with mud and water and bathing in rice paddies. The opportunity for exposure to the larvæ of hookworm was great. It is probable that all of these patients contracted hookworm infection in this theatre. Only one-fifth of the group had lived in the "hookworm belt" in the United States, and *A. duodenale*, a species uncommon in the United States, was recovered in high percentage. We have no reliable data on the actual incidence of hookworm infection among the troops who served in the forward areas, but it must have been considerable.

Treatment. The routine treatment consisted of a fat-free supper followed by a purge of 60 cc. of a saturated solution of magnesium sulfate. The next morning breakfast was omitted and 3 cc. of tetrachlorethylene in gelatin capsules were administered. A second purge was given 2 hours later.

An interval of 3 weeks was allowed to elapse between treatments. The second or subsequent vermifuge was usually tetrachlorethylene, although carbon tetrachloride (3 cc.) or hexylresorcinol (1 gm.) was sometimes substituted especially in resistant cases. The drugs were never given on the same day in combination.

No alarming symptoms appeared after the use of any of these drugs. A mild intoxication with manifestations similar to those produced by ethyl alcohol usually appeared about 20 minutes after tetrachlorethylene or carbon tetrachloride was administered.

When we first began to treat these patients, it was hoped that a single vermi-

fuge would be sufficient. However, it was soon found that the persistence of symptoms, associated with many eggs in the stools and a continued leukocytosis with eosinophilia, necessitated repeated treatments. In the absence of symptoms the continued presence of a few eggs or a slight eosinophilia was not considered an indication for repetition of the vermifuge. In all, the 50 patients received 110 doses of anthelmintic drugs.

Results of Treatment. The period of observation extended from a minimum period of 1 month when the results of treatment were favorable, to as long as 6 months in resistant cases. The patients have been analyzed from the standpoint of symptomatic improvement, the disappearance of eggs from the stools, and a reduction of the leukocytosis and eosinophilia.

A. Symptoms. At the time that treatment was instituted 43 patients had abdominal symptoms. At the conclusion of the period of observation, 9 patients (20%) were completely relieved, 23 (55%) were improved, and the remaining 11 (25%) denied any decrease in their symptoms. The complaints of anorexia, vomiting and diarrhea were most readily relieved. The cramping pain after meals was the slowest to disappear and was the symptom which persisted in those who were unimproved. In general the more stoical and emotionally stable individuals improved rapidly or were cured by 1 to 3 treatments. In most of these who were not improved after repeated vermifuges, the past history revealed either prior gastro-intestinal complaints of a functional nature, nail biting, enuresis or some other manifestation of emotional instability. Eventually after prolonged study, the unimproved group (11 patients) were reassigned from combat duty to other tasks. In every instance, psychoneurosis was considered the primary reason for reassignment and no patient was reassigned because of the resistant hookworm infection.

B. Stool Findings. One week or more after the last vermifuge 34 patients had

specimens examined by the concentration method. Of these 20 (63%) still showed hookworm eggs, although they had been treated an average of twice each.

C. Eosinophilia. The eosinophilia, as has been pointed out previously, varied considerably from count to count, but in general it decreased after the administration of a vermifuge. The degree of eosinophilia dropped from an average maximum of 13,700 leukocytes with 34% eosinophiles to 9600 leukocytes with 21% eosinophiles. In only 3 patients did the eosinophilia drop below 4% following treatment.

Discussion. The clinical picture of abdominal pain, vomiting and diarrhea in patients with a high eosinophilia and hookworm eggs in the stool occurred with a frequency to make us believe that these cases were true instances of acute hookworm disease. This is not the usual symptomatology ascribed to hookworm infection in which anemia dominates the picture, nor to the lesser infections where the symptoms are mild or non-existent. A number of factors may have influenced the picture of the disease as we have seen it. First, the patients were presumably previously uninfected individuals who had been exposed to the parasite over a short period of time. How much of their symptomatology may have represented a local allergic manifestation and how much may have been due to local irritation produced directly by the worms in the upper small intestine is a matter of conjecture. The very high eosinophilia in these patients suggests a considerable reaction to foreign protein. The circumstance of a previously unexposed group of young adult white males being exposed to *A. duodenale* may in itself, in large degree, explain the observations. A striking feature was the presence of incapacitating abdominal symptomatology occurring with a small worm burden. *A. duodenale* is recognized as causing a more severe form of hookworm disease than *N. americanus* and to produce symptoms with a smaller number of adult worms.³ A second possible factor has been the high incidence of intercurrent

disease and battle wounds. Relapsing vivax malaria, amebiasis, bacillary dysentery, typhus, and cutaneous diphtheria occurred in some of these patients. Debility from these diseases may have played a part in exaggerating the gastro-intestinal symptoms. A third factor was the situation in which the disease was contracted. In many instances the symptoms appeared shortly after the soldiers arrived in combat for the first time. The emotional stress, the restricted diet, and the physical fatigue undoubtedly caused an exaggeration of gastro-intestinal symptoms. Furthermore, once the patient was evacuated to the rear, either a conscious or subconscious effort to escape further combat duty may have increased the severity of the symptoms in many. The decision has been difficult to make as to whether a given individual was (a) malingering; (b) having symptoms chiefly as the result of intestinal parasites, or (c) whether his complaints were aggravated by, or entirely due to a psychoneurosis. When after repeated treatments a soldier continued to complain of abdominal pain and had, in addition, eggs in the stools and a persistently abnormal gastro-intestinal Roentgen ray pattern, he became a difficult medical problem. The weight of our experience indicated that after one or two vermifuges, hookworm infection should no longer be disabling. Every effort was made to minimize to the patient the importance of a few hookworm eggs in the stool and to discharge him to duty as soon as he became free of symptoms.

The difficulties in demonstrating hookworm eggs in the stools by the direct method were great. The effectiveness of the zinc sulfate flotation-centrifugation method for finding hookworm eggs should be stressed. It was not at once presumed that the clinical picture observed could have been produced by the small wormloads noted, but only after thorough consideration of many detailed clinical histories. Until this method was put into routine practice there were a large number of patients on the wards of this hospital.

with unexplained abdominal pain associated with eosinophilia. Even with the help of this improved laboratory technique, a small number of patients in whom we suspected hookworm infection had repeatedly negative stools. In a few patients not included in this study who had consistently negative stools prior to treatment, adult worms were recovered following the vermifuge. In specimens from other patients, eggs were not demonstrated until a vermifuge had been given. In many, eggs were found only intermittently.

A period of time necessarily elapses from the entrance of the larvæ through the skin and the appearance of eggs in the stools. In 1 patient eggs were demonstrated as early as 1 month after the probable date of exposure. In a number of patients, difficulties in proving the presence of the parasite may have been due to the fact that not enough time had passed for full development of the adult worms. We suspected that the eosinophilia appeared before eggs were passed in the feces. No data concerning this point are available in this series of patients.

The drugs used in the treatment of this group of patients: tetrachlorethylene, hexylresorcinol, and carbon tetrachloride probably removed the majority of the worms. By so doing, these anthelmintics probably prevented an anemia and relieved patients of most of their symptoms. In civilian practice this has apparently sufficed, but in military practice a more effective vermifuge is desirable. However, it is stated that *A. duodenale* infections are more refractory to therapy than *N. americanus* infections.⁴ In the first place a drug which could have eliminated all the hookworms in a single treatment would have prevented the prolonged hospitalization required in this group of patients in whom 2 and 3 treatments were necessary. Since 3 weeks were permitted to elapse between each treatment a soldier had to be hospitalized at least 6 weeks to be treated 3 times. The second reason why a more effective drug is needed is that the per-

sistence of hookworm eggs in the stools erects a stumbling block which impedes the rapid recognition of functional disease or malingering and therefore delays the proper disposition of patients. It is agreed, however, that for practical purposes, the aim of treatment with drugs at present available, need not be the removal of all adult worms.

Some mention should be made of strongyloidiasis because it may produce a very similar clinical picture of abdominal pain and diarrhea with a very marked eosinophilia. The gentian violet treatment, both with enteric-coated tablets and duodenal instillation of the drug, has been ineffective in eliminating this parasite. Enough symptomatic improvement occurred over a period of 2 or 3 weeks in most instances so that the patients were returned to duty even though they were still passing occasional rhabditiform larvæ.

In conclusion in presenting this group of cases of hookworm infection we do not wish to imply that we believe all soldiers who acquire the infection have the more acute symptoms which have been described. Many additional cases of entirely asymptomatic hookworm infection have been discovered in patients who were admitted for some unrelated disease. It is our belief that a large number of men who have lived under combat conditions in this theatre have hookworm infection. This group of 50 patients includes soldiers who have been most heavily infected, those who have reacted most violently to the presence of these parasites, and those in whom any illness might precipitate a psychoneurosis.

Summary. 1. In this theatre, a relatively acute syndrome of abdominal pain, anorexia, nausea, vomiting, diarrhea, and weight loss was observed in soldiers who had a marked eosinophilia and hookworm infection. The symptoms were believed to have begun within a few weeks after the penetration of the skin by the larvæ and to have persisted for several months in a diminished degree.

2. *A. duodenale* infections predominated. The severity of the clinical symptoms was considered disproportionate to the worm burden, which was judged to be small.

3. The initial direct stool examination revealed hookworm eggs in only 20% of the patients. By repeated direct examinations it was possible to establish the diagnosis in a little more than half. The zinc sulfate flotation-centrifugation method proved a rapid and efficient means of finding eggs in the stool, increasing the number of positive examinations approximately four-fold.

4. Tetrachlorethylene, carbon tetrachloride, and hexylresorcinol have not proved

entirely satisfactory as vermifuges since they were unable to eliminate all the parasites even when given repeatedly. This has resulted both in prolonged hospitalization and in delay in the proper disposition of those patients who had little inclination to return to duty.

5. Most textbook descriptions of hookworm disease present a clinical picture dominated by anemia and malnutrition. In the light of these observations, it is clear that hookworm disease in white young adults may be an acute enteritis before anemia and malnutrition develop; the diagnosis can often be suspected clinically at this stage, on the basis of the phenomena described in this report.

REFERENCES

1. BELDING, D. L.: Textbook of Clinical Parasitology, New York, Appleton-Century, p. 293, 1942.
2. FAUST, E. C., *et al.*: A Critical Study of Clinical Laboratory Techniques for the Diagnosis of Protozoan Cysts and Helminth Eggs in Feces, *Am. J. Trop. Med.*, **18**, 169, 1938.
3. KEEFER, GEORGE P.: The Small Intestine in Acute and Subacute Hookworm Disease. (To be published.)
4. STRONG, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, Philadelphia, Blakiston, p. 1268, 1944.

RUTIN: A NEW DRUG FOR THE TREATMENT OF INCREASED CAPILLARY FRAGILITY

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RUTIN is a crystalline glucoside of quercetin derived from buckwheat leaves and blossoms, tobacco leaf, rue herb, tomato stems, white hydrangea,³ yellow pansies, the leaves of the common elderberry, and many other flowers and leaves. Chemically, it is a rhamnoglucoside of quercetin, thus being a derivative of flavone. Flavone, in turn, is a derivative of gamma-pyrone and from it are formed various yellow dyestuffs. Citrin is an impure mixture of two flavone glucosides, hesperidin and eriodictyol, which, in association with vitamin C, have been thought to regulate vascular permeability. This factor, supposed to regulate capillary permeability, also has been named vitamin P.¹

Citrin was prepared by Szent-Györgyi in 1936 from lemons or paprika and he found that this compound corrected experimentally produced increased capillary fragility in guinea pigs. However, the crystalline glucosides, hesperidin and eriodictyol, have been found to be physiologically inert, while the active compound in these crude glucosides never has been discovered. Although it never has been proven, the probability exists that the active substance is rutin.

The close relationship between hesperidin and rutin can be seen by inspection of their structural formulæ:

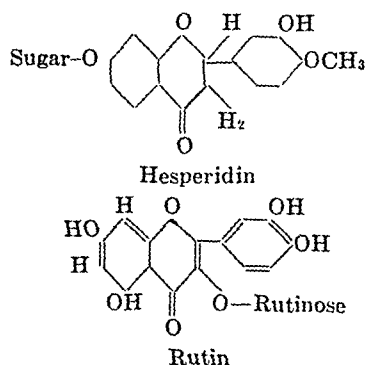


FIG. 1.—Structural formulas of hesperidin and rutin.

The drug, rutin, shows neither acute nor chronic toxicity to laboratory animals and, on this basis, its effects were tried on man. It was found that patients treated with daily doses of rutin for as many as 16 months showed no toxic effects attributable to the drug.⁴

Material. The rutin used in this study was prepared by the Eastern Regional Research Laboratory of the U. S. Department of Agriculture. It is prepared by alcohol percolation from green buckwheat. The drug is a bright yellow powder consisting of needle-shaped crystals melting at 192 to 196° C. and decomposing at 214° C. It is sparingly soluble in water: 0.13 gm. per liter at 20° C. and more in boiling water. It is soluble in methanol, ethanol, pyridine, acetone, ethyl acetate and alkalies. It is insoluble in chloroform, ether and hydrocarbons. It can be hydrolyzed with dilute acids to quercetin, glucose and rhamnose.²

Rutin is superior to crude hesperidin in that the rutin may be purified by recrystallization, thus making assay and accurate dosage possible.

The patients studied were taken from the private practice of the author, with one exception, and consist mainly of hypertensive subjects who had been studied according to Griffith's⁶ method. He has suggested "that an abnormal condition of the capillaries might be a factor in the production of certain of the vascular accidents which sometimes occur in cases of hypertension."⁵ The method also was used as a control of vascular complications in the thiocyanate therapy of hypertension and in several cases of unexplained bleeding associated with increased capillary fragility.

Method. *Capillary fragility* was measured by Gothlin's technique. A description of this method taken from Griffith and Lindauer⁵ follows:

"Technique of the Test:—(1) Mark off a circular area, 6 cm. in diameter, in each antecubital area. Mark off all blemishes and marks in this area that might later be

confused with petechiæ. (2) Place a standard blood pressure cuff about each arm, and maintain in each a pressure of 35 mm. of mercury for 15 minutes. Lower the pressure, and count and mark all petechiæ within the two circular areas, using a good light and a magnifying lens of 5 D or its equivalent. (3) One hour or more later, repeat, using a cuff pressure of 50 mm. of mercury.

"The Petechial Index is calculated as follows: To the number of petechiæ occurring at 35 mm. of mercury multiplied by 2, add the additional number occurring at 50 mm. Based upon the Petechial Index, capillary fragility is regarded as: (a) normal, if the Index is 8 or less, (b) increased (abnormal) if the Index is 13 or more, and (c) borderline, but probably abnormal, if the Index is 9 to 12. In order to save time, the second stage can be omitted under the following conditions: (1) The number of petechiæ after the first stage is 2 or less. Such persons may be considered normal. Usually, but not invariably, the person is normal who has 3 petechiæ after the first stage. (2) If 6 or more petechiæ appear after the first stage, the subject may be considered abnormal. (3) The test is a repetition, and may be compared with the corresponding first stage of an earlier test. Repetition is less than 3 weeks, however, is unreliable in any case. The second stage should always be done if the fragility is being tested in a subject for the first time and there are 4 or 5 petechiæ after the first stage. It should also be done in most cases when the number after the first stage is 3."

Dosage. The dosage of rutin used was 20 mg. 3 times daily. A few patients who did not respond to this dosage were given 40 mg. 3 times daily.

In each case of the hypertensive and thiocyanate subjects a complete history was taken and a detailed physical examination including chest fluoroscopy, electrocardiogram, eye ground examination, and kidney function studies, was done. This was simply a matter of selection to rule out any other serious organic disease. The series comprises 32 cases divided as follows:

1. Hypertension—24.
2. Thrombopenic purpura—1.
3. Pulmonary hemorrhage with increased capillary fragility—2.

4. Complete heart block with retinal hemorrhage—1.

5. Nuclear lesion of the eighth nerve—1.

6. Increased capillary fragility due to drugs—3.

(a) Sulfadiazine—1.

(b) Gold salts—1.

(c) Acetyl salicylic acid—1.

GROUP 1. The first group consisted of 24 hypertensive subjects. Of these, 13 were persons who showed increased capillary fragility ranging from an index of 10 to 20 (average 16). The remaining 11 consisted of patients with hypertension being treated with potassium thiocyanate. For convenience these are being described in subgroups. (a) In the group of 13 cases repeat determinations of capillary fragility were made within 3 to 4 weeks after the institution of rutin therapy. Observation has ranged from 6 weeks to 9 months. The 13 cases showed an improvement within the initial 3 weeks period. Two of these became normal within this period, while all became normal within 12 weeks and have remained normal to the present time. None of the group has had any demonstrable vascular accident during the period of treatment. (b) There were 11 patients being treated with potassium thiocyanate for hypertension. Seven of these cases with capillary fragility originally normal were given rutin and thiocyanate coincidentally and the Gothlin Index remained normal. Three cases with capillary fragility initially normal were given potassium thiocyanate alone and developed an increased fragility. Rutin was added to the treatment and capillary fragility became normal. One case with an increased index was given rutin and followed by thiocyanate. The index became normal and remained so.

GROUP 2. One case of essential thrombocytopenic purpura was treated with rutin without benefit for a period of 2 weeks, which may have been an insufficient interval. The patient was too ill to permit a longer trial, and splenectomy was performed with subsequent recovery.

GROUP 3. Two cases showed recurrent pulmonary hemorrhages of variable amounts. Both were studied extensively including bronchoscopy and bronchograms with no demonstrable pulmonary lesions being found. Capillary fragility in both cases was increased. Because of the interesting features of these cases, brief summaries of their clinical features are presented.

Case Abstracts. CASE 1. J. B., aged 38, a white female housewife, complained of bleeding from the mouth for 3 months. The bleeding was about 1 drachm at a time and occurred 3 to 4 times a week. Bronchoscopy revealed nothing positive except a small suspicious area covered with blood in one bronchus. Bronchograms showed no pathology from a Roentgen ray standpoint. Blood examination: 3,930,000 erythrocytes; 13 gm. hemoglobin; cell volume of 41%; 255,450 platelets; 4300 leukocytes (55% neutrophils, 4% eosinophils and 41% lymphocytes). Sedimentation rate was 21 mm. in 1 hour by the Wintrobe method; prothrombin time was 30 seconds, or 83% of normal. Gothlin Index was 17. Treatment was started with 20 mg. of rutin 3 times a day. At the end of 3 weeks the Gothlin Index was 6 and bleeding had ceased. During the second 3 weeks there was no bleeding and there has been none reported after 6 months.

CASE 2. M. S., aged 20, a white female, was seen with a complaint of massive pulmonary hemorrhages over a period of 3 years. The first of these followed 1 week after an automobile accident in which she received a bump on her sternum. There have been 6 recurrences in which the bleeding was profuse. The patient was studied in 1942 by Dr. L. H. Clerf who reported as follows:

"At that admission it was thought that the blood was vomited. X-rays of the gastrointestinal tract and of the chest were negative. Esophagoscopy was negative. Bronchoscopy was negative except that some blood tinged secretion was seen coming from the right lower lobe bronchus, but this was observed on only one occasion and no apparent cause could be discovered. Hematologic studies revealed no blood dyscrasia, except a low hemoglobin and red blood cell count following a recent hemorrhage. Iodized

oil was instilled to determine if there was bronchiectasis. Several of the sub-divisions of the right lower lobe bronchus revealed incomplete filling due apparently to the presence of some obstruction, particularly clotted blood. The remainder of the tracheo-bronchial tree appeared normal."

In April, 1945, she was studied in the Medical Ward of the University of Pennsylvania Hospital (service of Dr. O. H. Perry Pepper). Here, 3 days after admission, the patient coughed up 80 or 90 cc. of bright red blood. Immediate examination by an otolaryngologist showed the blood was coming from the respiratory tract, and not from the nose, mouth or larynx. Bronchoscopy showed blood in the trachea, but no source of bleeding. The patient was bronchoscoped 3 times and lipiodol twice was instilled and the entire tracheobronchial tree mapped out by Roentgen ray, but no lesion was discovered. Physical examination was negative. Other studies included: Platelets, normal, 202,000 in number. Prothrombin time 95% of normal. Bleeding and clotting times both normal. Blood count: hemoglobin 84%; red blood cells, 4,600,000; white blood cells, 6000 to 10,300, with a normal differential count: neutrophils, 63 to 68%; lymphocytes, 19—31%; mononuclears, 9%; eosinophils, 3%; basophils, 1%. Serum proteins, 6.8 gm.; serum cholesterol, 203 mg. %, fasting blood sugar, 82 mg. %; blood urea nitrogen, 10 mg. %; BMR + 5%. Sedimentation rate was 35 mm. per hour, which, by the method used, was slightly increased. Serology was negative. Repeated urinalyses showed occasional white cells, but nothing else. The tuberculin test was barely positive.

Fragility studies were done by the author and capillary fragility, measured by the method of Gothlin, was increased, 10 petechiae appearing after the first stage of the test. The patient was placed on rutin, 20 mg. t.i.d., and discharged May 19, 1945. She was readmitted July 11, 1945, and stated that she had had no more bleeding episodes since the last admission. Capillary fragility was normal, only 2 petechia appearing after the first stage of the Gothlin Test. Chest Roentgen ray and bronchoscopy were repeated, and were unchanged. The rutin was continued. The patient volunteered the statement that she felt better than she had felt for 3 years.

GROUP 4. One patient, with complete heart block and a blood pressure of 280/160, suffered a massive hemorrhage of the retina resulting in blindness except for light perception. Capillary fragility was 20 and there were numerous dime-size areas of ecchymosis of the extremities. This patient was given 20 mg. of the drug 3 times a day with reduction of the index to normal and its maintenance within normal limits after 5 months. An occasional ecchymosis is seen but there has been no retinal involvement of the good eye. There has been no effect on blood pressure.

GROUP 5. Another case presented with evidence of a small nuclear lesion of the eighth nerve. The Gothlin Index was 14 which was reduced to 2 after 3 weeks of rutin therapy.

GROUP 6. A group of 3 cases showed increased capillary fragility as a result of drug sensitivity. One had a diffuse purpuric rash as a complication of sulfadiazine. Bleeding from the gums and urinary tract also occurred. The drug immediately was withdrawn and therapy with rutin started. Within 3 days external bleeding stopped and no new purpuric spots were noted. A similar experience was noted after the use of gold salts for rheumatoid arthritis. Whether the withdrawal of the drug or the use of the rutin was the effective therapy is a question. A third case seemed to have increased capillary fragility from the use of aspirin. The coincidental use of rutin with aspirin did not improve the state of the capillaries, for, on one occasion, a single dose of 20 gr. of aspirin, taken independently by this patient, while on rutin, produced a severe allergic reaction marked by urticaria, vasomotor rhinitis, and many small capillary hemorrhages about the shoulders and arms. Capillary fragility determination showed the index to be 4 which is well within the limits of normal. From this study it would seem that the reaction of the capillaries in the group termed "allergic purpura" is different from that in the group showing increased

capillary fragility and one can infer that the value of rutin could be questioned in the allergic cases.⁷

Summary. 1. The drug, rutin, was used in a series of cases showing increased capillary fragility under a variety of circumstances.

2. The drug is non-toxic for man.

3. Results are reported in the following cases:

A. *Hypertension.* A group of 24 cases divided into 2 subgroups was chosen. Subgroup (a) consisted of 13 cases with increased capillary fragility all of which were improved with rutin. Subgroup (b) consisted of 11 cases treated with thiocyanate and rutin; 7 of these had normal fragility which was maintained by the prophylactic use of rutin given coincidentally with thiocyanate; 2 cases on thiocyanate alone developed an increase in the Gothlin Index which became normal following treatment by rutin; 1 case originally showing an increased index was given rutin followed by thiocyanate when the index became normal and was maintained subsequently at a normal level.

B. Two cases of *pulmonary hemorrhage* of undetermined origin, with increased capillary fragility, were given rutin with cessation of bleeding and a return to normal of the Gothlin Index.

C. Three cases of increased capillary fragility due to drug reactions were treated with uncertain results.

D. One case of small hemorrhage into the eighth nerve nucleus, and 1 with complete heart block and retinal hemorrhages were studied. Both showed increased capillary fragility which returned to normal following medication by rutin.

Conclusions. The drug, rutin, has an action on capillaries, which action appears to be equal to or possibly superior to that shown by members of the hesperidin group. This action is demonstrated in the cases here reported showing increased capillary fragility. With due regard to the relatively small number of cases and short periods of observation, it is reason-

able to conclude that the drug appears to be of value in: (1) preventing vascular accidents in patients with hypertension; (2) maintaining normal capillary fragility, and hence the avoidance of vascular accidents in patients being treated with thiocyanate; (3) controlling pulmonary bleeding when no other cause is apparent.

REFERENCES

1. ARMENTANO, *et al.*: *Deutsch. Med. Wchnschr.*, **62**, 1325, 1936.
2. COUCH, J. F., and KREWSON, C. F.: *Bureau Ag. and Ind. Chem.*, Mimeograph 52, 1944.
3. COUCH, J. F., and NAGHSKI, J.: *J. Am. Chem. Soc.*, **67**, 1419, 1945.
4. GRIFFITH, J. Q., JR., COUCH, J. F., and LINDAUER, M. A.: *Proc. Soc. Exp. Biol. and Med.*, **55**, 228, 1944.
5. GRIFFITH, J. Q., JR., and LINDAUER, M. A.: *Am. Heart J.*, **28**, 758, 1944.
6. GRIFFITH, J. Q., JR., ROBERTS, E., and CORBIT, H. O'BRIEN: *Am. Heart J.*, **21**, 47, 1941.
7. RAPAPORT, H. G.: *J. Pediat.*, **18**, 321, 1941.

ACUTE ETHYLENE GLYCOL POISONING

A CLINICO-PATHOLOGIC REPORT OF EIGHTEEN FATAL CASES

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THE ingenuity displayed by some in finding substitutes for alcoholic beverages is remarkable, as evidenced by this report which deals with 10 soldiers who drank lethal quantities of anti-freeze solution of the ethylene glycol (Prestone) type. The opportunity to study such a group is seldom to be had, if one may judge from the paucity of literature on human cases. Nearly all of the papers on ethylene glycol poisoning have been concerned with experimental toxicology and, even in these, descriptions of pathologic changes have been brief and incomplete.^{3,4,7,8,9}

Ethylene glycol ($\text{HO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}$) is a colorless, odorless liquid which evolves heat when mixed with water. It possesses a rather pleasant, bitter-sweet flavor and when swallowed imparts a warming sensation to the tongue and esophagus. After ingestion the compound is oxidized, at least in part, to oxalic acid; urinary oxalates are increased and crystals of calcium oxalate are deposited in the kidneys. The minimum lethal dose for human beings has been estimated at about 100 cc.^{5‡}

The most spectacular postmortem finding in acute ethylene glycol poisoning, both in man and experimental animals, is the extensive oxalate "crystallosis" of the renal tubules. Observations such as Brekke's² in attributing recovery in his 2 cases to unilateral decapsulation of the kidney have led to the belief that death results from renal damage, even though the outstanding symptoms are indicative of central nervous system damage. We suggest that the operation did not con-

tribute much to the survival, but rather that the patients had consumed a sublethal amount of ethylene glycol.

Boemke¹ is the only author who has described significant structural changes in the brain, even though he has not been inclined to attach much importance to them. He noted generalized hyperemia of the brain and leptomeninges in 2 of his 4 cases; small ring hemorrhages in the brain stem and cerebral white matter were seen in 1 of these, as well as a perivascular cell infiltrate in both gray and white matter of the cerebrum. Boemke regarded the cellular reaction as residual from a previous infectious disease, such as typhus, and the hemorrhages as due to action of the chemical to increase the permeability of already weakened vessel walls. The brains in our series of previously healthy soldiers displayed all gradations of change, from simple hyperemia and edema to severe chemical meningo-encephalitis, and Boemke's explanation is thereby refuted.

Clinical Data. Due to the urgent need for treatment, the short course, and the field conditions under which most of the patients were observed, clinical notes and laboratory studies were meager and in 2 cases completely lacking.

The patients were all males ranging in age from 20 to 33 years; 6 were white and 4 Negro. Death occurred in from 22 to 44 hours after ingestion of the fluid except in 1 instance. This man drank several glasses of "vodka" and, although a companion§ "passed out" 10 hours later, the

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‡ The amount consumed was 200 cc. in 1 of our cases, unknown in the others.

§ We were unable to trace this case.

onset of his symptoms was delayed for 2 days and he lived 3 days thereafter. The men were not observed in the initial stages of the intoxication, but 1 had a history of early vomiting which subsided, and 2 continued to vomit until death.

or 12 hours, probably within the first few hours. The single exception was the soldier already mentioned whose symptoms were delayed; coma developed late after a period of restlessness and delirium. Two of the patients had incontinence of urine and feces; 4 had severe convulsive

TABLE 1.—COMPARISON OF CERTAIN CLINICAL DATA WITH CENTRAL NERVOUS SYSTEM LESIONS IN 10 CASES OF ACUTE ETHYLENE GLYCOL POISONING*

Case No.:	I	II	III	IV	V	VI	VII	VIII	IX	X
Age	20	28	21	21	30	30	..	33	24	20
Race	W	W	W	W	N	N	N	W	N	W
Sex	M	M	M	M	M	M	M	M	M	M
Lived (hrs.)	44	24	24	28	22	41	120	43	32
Temperature (°F.) . .		98-102	†	†	93	93	93-102			
Pulse		96	120	130	64	54	42-108			
Respiration			30	30	..	5-10	5-10			
Blood pressure . . .		160/112	108/40	140/80	110/40	190/140	120/40			
Coma		Early	Early	Early	Early	Early	Early	Late	Early	
Convulsions				Late	Late	..	Yes	..	Late	
Incontinence			Yes	Yes						
Strabismus							Yes	Yes	Yes	
Nystagmus			Yes		
Reflexes:										
Deep		0	0	0					0	
Pupillary		+	+	+	0	0	0			
Corneal					+					
Brain lesions:										
Hyperemia	+++	+++	++	+++	++	++	+++	+++	++	+++
Edema	+++	+++	++	+++	++	++	++	++	++	+++
Hemorrhage	+	0	0	+	0	+	+	+	+	+++
Cell degeneration .	++	+	+++	++	+++	+	++	++	++	+++
Encephalitis	0	0	0	0	+	0	+++	+++	++	0
Meningitis	0	0	0	0	++	+++	+	0	±	0
Crystals	+	+	±	±	++	+++	++	++	+	+

* Spaces left blank indicate that the item was not mentioned in the clinical record. Items marked ± imply a positive finding, but too slight in degree to warrant + designation.

† Temperature not recorded, but patient described as "cold and clammy."

The body temperatures tended to be low, 2 patients having been described as "cold and clammy," and 3 had rectal temperatures of 93° F. One of the latter and another man with a normal temperature had a subsequent rise to 102° F. No readings on the remaining 4 were recorded. The pulse rate ranged from 42 to 120 and the respiration from 5 to 30 per minute, but the two did not always follow the temperature curves. Blood pressure varied from 108/40 to 190/140, the highest being observed in a patient with a temperature of 93° F., pulse 54, and respiration 5. Eight cases presented the clinical appearances of shock.

All but 1 of the men were discovered in deep coma which had supervened at some unknown time within the first 10

seizures toward the end; 3 displayed strabismus; 1 also had vertical and lateral nystagmus. Deep reflexes were absent in the 4 cases tested, although the pupillary reactions could still be elicited. In 3 other cases the pupils were fixed and in 1 only a slight corneal reflex was obtained.

Laboratory Data. The urine was examined in 5 cases and invariably contained oxalate crystals; a trace of albumin was present in 4, a heavy cloud in the 5th, in which survival was longest. A few leukocytes were noted in the urinary sediment, but no red blood cells or casts.

A blood count was performed in only 1 case, erythrocytes being 7,370,000, hemoglobin 17 gm. and leukocytes 47,900 (86% neutrophils). The non-protein nitrogen level was 47 mg. per 100 cc.* and

* In a case not included in the series because the brain was not examined, the non-protein nitrogen value was 43 mg. per 100 cc.

blood sugar 240 mg., the latter rising to 400 mg. in several hours despite the administration of $\frac{1}{6}$ M. lactate and insulin. This patient was thought to be in diabetic coma until the urine was found to be sugar-free and the CO₂ combining power 46 vol. %. A sample of blood taken 4 hours after death in another case contained 76.9 mg. urea nitrogen per 100 cc.; the validity of this figure is questioned, however.

The *spinal fluid* was described as clear in 3 cases, while in 4 it was blood-tinged. The specimen from the patient with the high blood sugar levels was clear, contained 1 cell per c.mm. and 92 mg. of sugar per 100 cc., and was under a pressure of 160 mm. of water.

Gross Pathologic Findings. The tissues in general were congested and in all cases there was moderate to marked pulmonary edema. The *kidneys* were somewhat swollen and weighed from 200 to 260 gm. in all the cases except the one of longest duration in which each approximated 300 gm. The parenchyma was pallid and prominently striated by engorged vessels, but the markings remained distinct; the pelvic mucosa occasionally showed small patches of hemorrhage. The weight of the *liver* was normal except in 3 instances in which it was recorded as 2100, 2125 and 2350 gm. The organ was occasionally described as soft or flabby, but displayed no distinctive gross change. Injection of the meninges was recorded in 4. Six of the *brains* were prominently hyperemic, 2 of them presenting frank petechiae; 2 others were regarded as grossly edematous with distinctly flattened convolutions. Five weighed between 1500 and 1600 gm., 3 weighed 1400 to 1500 gm.; the other 2 were not weighed. The cerebrospinal fluid was thought to be excessive in 2 cases. The other organs showed no macroscopic lesions of note.

Histopathologic Observations. The gross finding of pulmonary edema was confirmed, with early bronchopneumonia pres-

ent in 6 cases. Crystals of calcium oxalate* were conspicuous throughout all of the *kidneys* (Figs. 1 and 2), occasionally in glomerular spaces, but for the most part in the renal tubules, sometimes seeming to pierce their walls. Despite this, there was no reaction to their presence in the 9 rapidly fatal cases apart from occasional slight epithelial desquamation. The tubular epithelium did not appear degenerate. The capillary bed was markedly engorged in common with the other tissues. In the kidney of the patient who survived 120 hours there was moderate degeneration of tubular epithelium, especially in the proximal convoluted segments, as well as edema of the interstices; the glomeruli remained apparently normal and there was no cellular reaction. His *liver* weighed 2350 gm. and displayed marked fatty change which was undoubtedly preëxistent; the same condition obtained to a lesser degree in the 2 other enlarged livers. There was evidence of mild parenchymatous degeneration in 2 other instances, but in general the organ was merely congested.

The fine capillary bed of the *brain* in every case was more conspicuous than usual and the larger vessels were engorged. Edema was evident in all to varying degrees, being very pronounced in 2. Perivascular hemorrhage was minor in 6 (Fig. 3 a) and prominent in 1 (Fig. 3 b). Early acute encephalitis was observed in 2 of the brains (Fig. 4), while in 2 others the inflammatory process was well developed (Figs. 5, 6 and 7). There was an associated meningitis in 3 (Figs. 10 and 12) and a 4th showed pronounced meningitis without encephalitis. The inflammatory exudate was perivascular in the brain and tended to be more diffuse in the leptomeninges. Neutrophils comprised the bulk of the cellular components of the exudate, although there was a distinct histiocytic reaction and an interspersion of lymphocytes.

Unfortunately, the entire brain was not

* The identity of the crystals was confirmed by Mr. William L. Eisenberg, Division of Microbiology, Food and Drug Administration.

available for study in any of the cases, our material being restricted to relatively small blocks of tissue submitted by the laboratory officers who performed the autopsies under the difficulties of field conditions. An evaluation of damage to

individual cells in the various regions and nuclei could not consistently be carried out; however, our observations make certain generalizations possible. In the cerebral cortex some of the ganglion cells, especially the Betz cells, displayed moder-

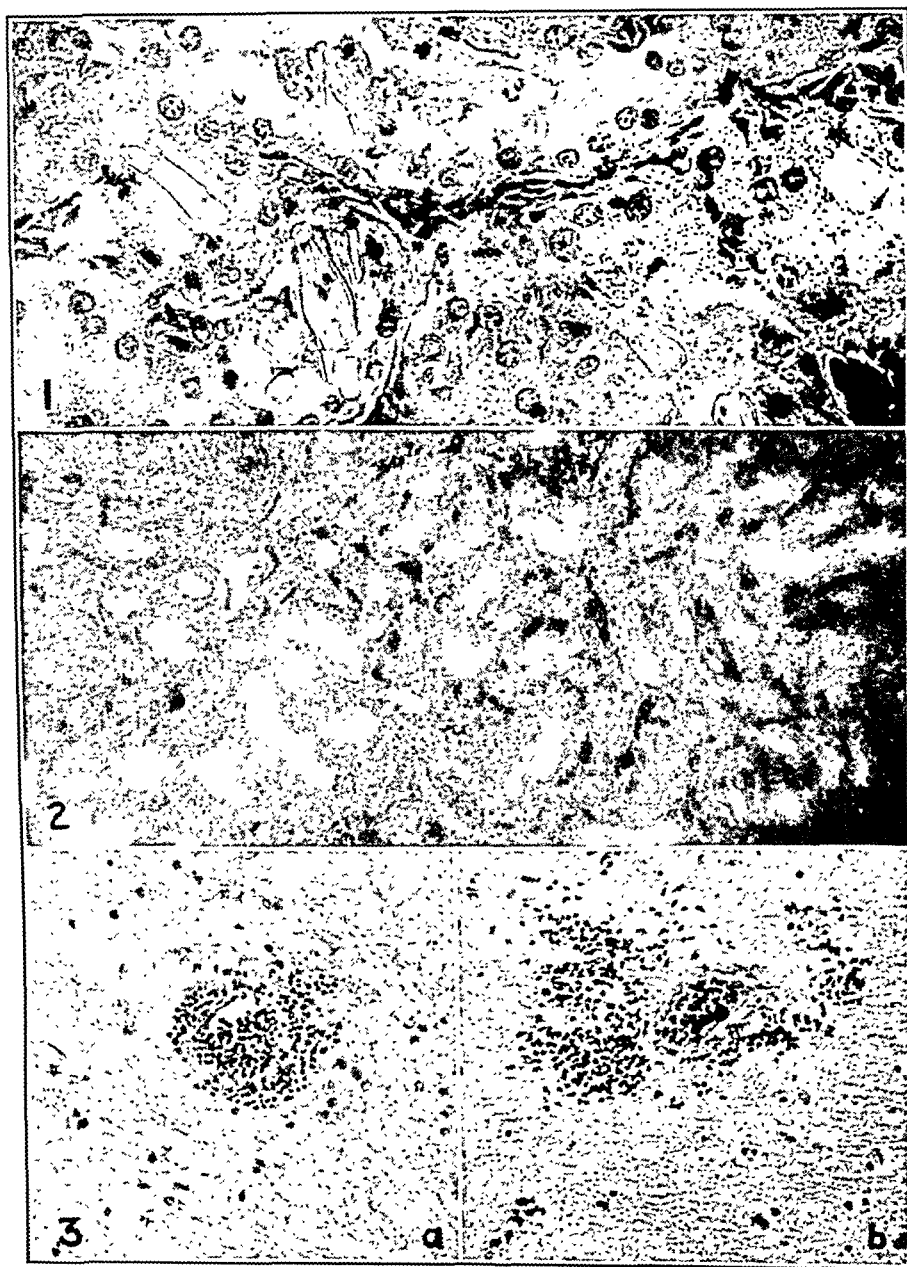


FIG. 1.—Heavy deposit of calcium oxalate crystals in renal tubules, a consistent finding. The uppermost tubule displays a loss of a few lining cells, there being little damage as the patient died within 48 hours. ($\times 600$ slightly reduced.)

FIG. 2.—The same kidney viewed with polarized light shows the wide distribution of the doubly-refractile calcium oxalate crystals. ($\times 145$.)

FIG. 3.—*a*, Early perivascular hemorrhage and marked edema in the white matter of the brain. Survival time, 22 hours. ($\times 250$ slightly reduced.) *b*, Damaged vessel wall and more diffuse hemorrhage. Survival time, 32 hours. ($\times 250$.)

ate chromatolysis and occasional loss of nucleoli and nuclei; satellitosis beyond the normal was sometimes encountered and was most prominent in the case of longest duration. The same alterations were observed in ganglion cells of the brain stem and cerebellum, a few displaying coagula-

tion necrosis, others faded to ghost forms. Perhaps the most striking change was the loss of Purkinje cells of the cerebellum and the evident damage to many of those that remained (Fig. 9).

Histologic examination with *polarized light* served to emphasize the extensive

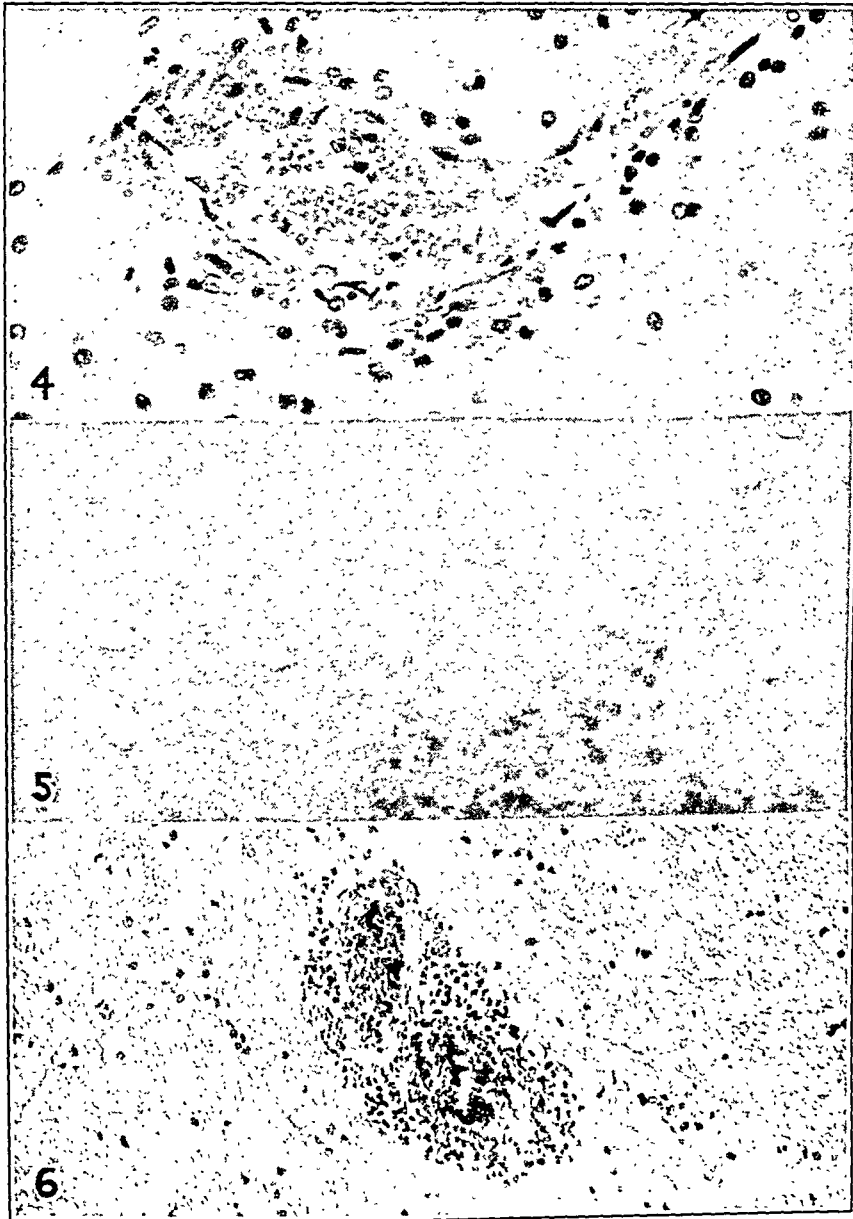


FIG. 4.—Beginning encephalitis, slight perivascular hemorrhage, and marked edema. Survival time, 28 hours. ($\times 500$ slightly reduced.)

FIG. 5.—The same field with polarized light disclosing otherwise invisible crystals, presumably oxalate. ($\times 500$ slightly reduced.)

FIG. 6.—Well-developed encephalitis, the cellular exudate being composed largely of neutrophils. A few crystals were demonstrated with polarized light. Survival time, 43 hours. ($\times 250$ slightly reduced.)

calcium oxalate deposit in the kidneys (Fig. 2), the crystals being doubly refractile. The same means disclosed similar but somewhat smaller crystals in the brain and leptomeninges (Figs. 5, 8 and 11), rather abundant in 4 cases and sparsely distributed in the others. For the most part they lay in the vessel walls and perivascular spaces, sometimes within the

vascular lumina. A few crystals were found in the brain substance proper where they evoked no glial or leukocytic reaction. They were clearly in the plane of the sections and could be readily distinguished from doubly-refractile particles occasionally present in the mounting medium employed. Furthermore, they could not be found in a control series

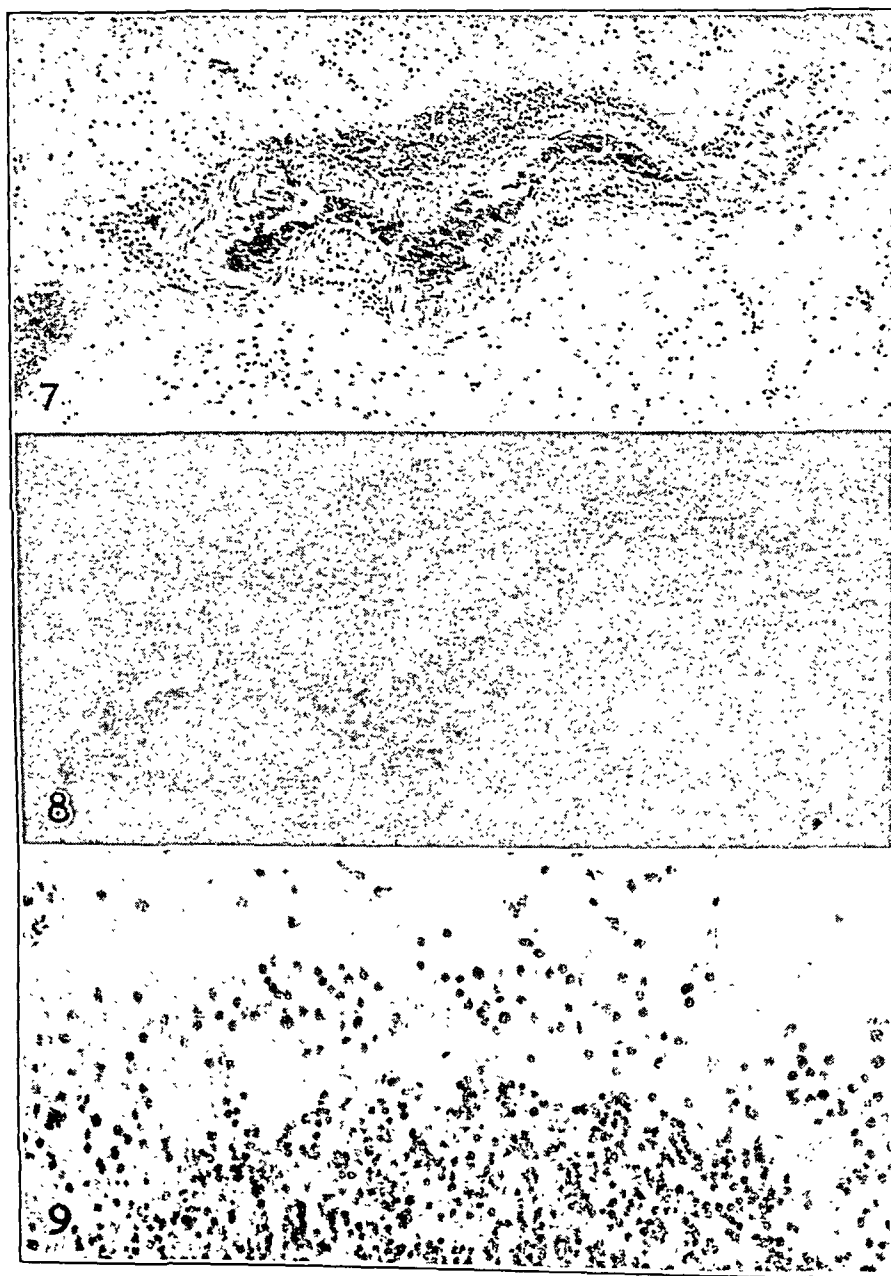


FIG. 7.—Severe encephalitis. Survival time, 41 hours. ($\times 135$.)

FIG. 8.—The same field with polarized light displays deposition of crystals. ($\times 220$.)

FIG. 9.—Cerebellum showing degeneration of Purkinje cells associated with edema and early proliferation in the Bergmann layer. Survival time, 32 hours. ($\times 300$.)

which consisted of brain sections from a group of unrelated conditions. A few isolated crystals were observed in the lungs, but virtually none in other organs.

Discussion. Symptoms referable to the central nervous system were the most conspicuous part of the clinical picture, as has been recognized by others. This

is in keeping with the histologic findings in our series, since there were significant intracranial lesions in all 10 cases, which varied from congestion and edema in the mildest to exudative meningo-encephalitis in the most severe.

Crystals, presumably oxalate analogous to the oxalate deposit in the kidneys, were

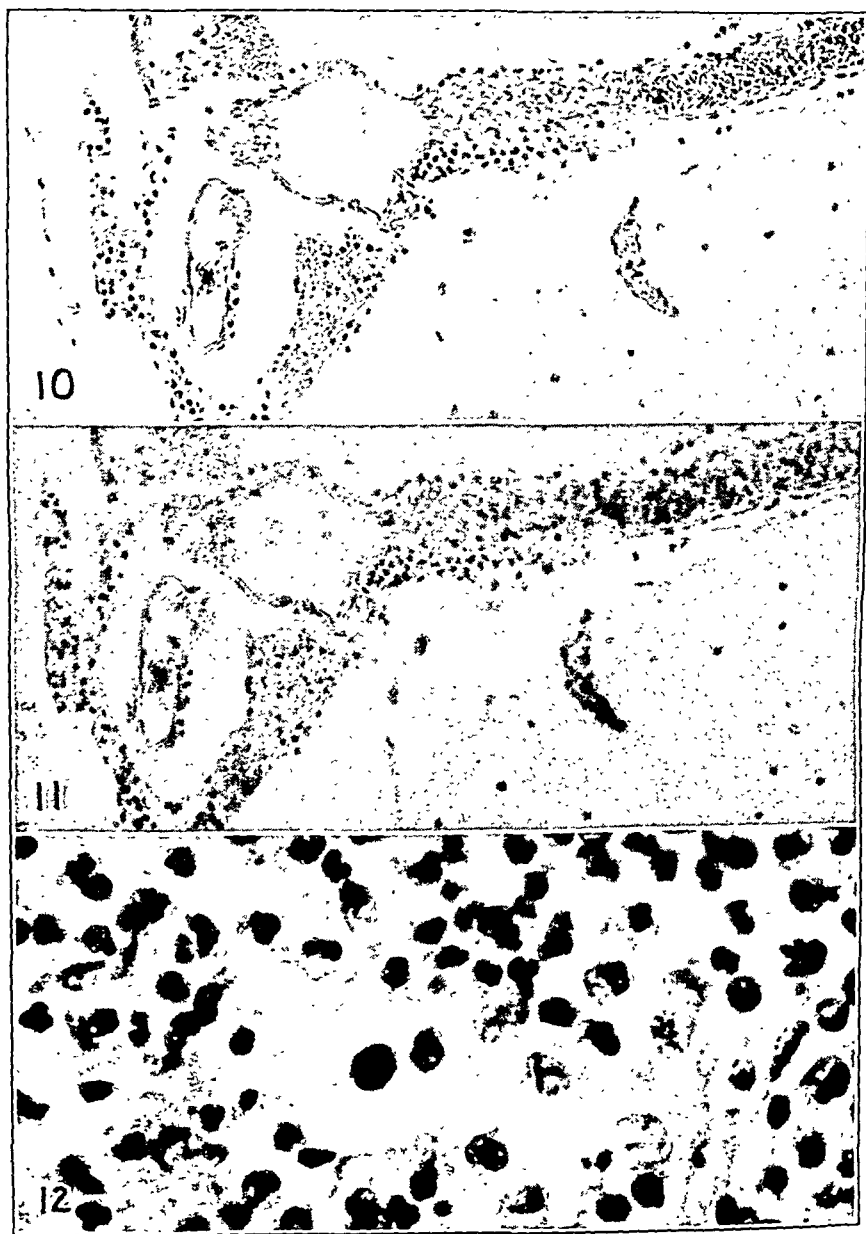


FIG. 10.—Early meningitis in which neutrophils comprise the bulk of the cellular exudate. Survival time, 43 hours. ($\times 250$ slightly reduced.)

FIG. 11.—Polarized light discloses large numbers of crystals in the section shown in Figure 10. ($\times 250$.)

FIG. 12.—Severe meningitis in which there is already an admixture of lymphocytes and histiocytes in the exudate. Survival time, 22 hours. ($\times 1000$ slightly reduced.)

observed in and about engorged vessels of the brain and meninges. It is probable that these crystals are here, as in the kidneys, oxidation products of ethylene glycol formed *in situ*.

The question can be raised as to why these two organs should be virtually the only sites of oxalate deposition. In the kidney, which is the main avenue of excretion of ethylene glycol, it is presumably a matter of concentration. If one may draw an analogy between ethylene glycol and ethyl alcohol as regards absorption, dispersion, and excretion, a possible explanation can be advanced regarding the brain. It has been shown that after administration of alcohol the blood level rises sharply during the 1st hour or 2 and gradually declines, whereas the alcohol concentration of the spinal fluid is built up more slowly but is sustained for a considerably longer time.^{8,10} Therefore, in the case of ethylene glycol, it may be of some significance that the crystals were found chiefly where tissue was in contact with cerebrospinal fluid, *i. e.*, in the pia-arachnoid and Virchow-Robin spaces.

Alterations of individual cells in formol-fixed brains are difficult to assess, particularly in older people and in whole brains fixed before slicing. In our series the degenerative changes described are regarded as valid, because all of the patients were young, most of the autopsies were performed soon after death, and small blocks rather than whole brains were placed in the fixative. Furthermore, the fact that some of the degenerating ganglion cells displayed satellitosis supports this view. We believe that damage to the central nervous system is due in part to a direct toxic effect of the chemical and in part to anoxemia resulting from circulatory disturbance, probably also of central origin.

With reference to the kidneys, it appears that if death occurs within 2 days renal

damage is minimal, despite the heavy oxalate deposit in the tubules. The single blood urea nitrogen level obtained in this group was high, but was probably not reliable as it was a postmortem sample; urinalyses showed only a trace of albumin. Significant renal changes were found in the patient who lived for 5 days, however, and the urine contained a heavy cloud of albumin.

The more complete data available in 1 case are of interest. There was evidence of hemoconcentration as judged from the blood count and, although the patient presented the clinical appearances of shock, his temperature was 98° F., pulse 96 and blood pressure 160/112. No explanation is offered for this inconsistency. The blood sugar values in this case were much higher than one can attribute to hemoconcentration and, whereas propylene glycol is converted to glycogen in the animal body, ethylene glycol is not. Glycogen may have been released as a result of liver damage, hardly apparent on histologic examination, or it is possible that ethylene glycol or some product of its intermediate metabolism may have acted as a reducing agent in the test for sugar.

Since this paper was prepared 8 additional cases of acute ethylene glycol poisoning have been observed. The clinical and pathologic findings were identical with those described in the 10 original cases.

Conclusions. Acute ethylene glycol poisoning produces demonstrable lesions of the central nervous system and by this means is responsible for death, as shown in each of 10 fatal cases reported here, and 8 more mentioned in the addendum.

Renal damage severe enough to contribute to a fatal outcome was found in only 1 patient who survived for 5 days; in the other cases there was nothing beyond simple deposition of calcium oxalate.

REFERENCES

1. BOEMKE, F.: Beitrag zur Toxikologie und Pathologie des Aethylenglykols (Glysantin), *Virchows Arch.*, 310, 106, 1943.

2. BREKKE, A.: Two Cases of Ethylene Glycol Poisoning, *Norsk. Mag. f. Lægevidensk.*, **91**, 381, 1930.
3. BROWNING, E.: Toxicity of Industrial Solvents, Med. Res. Council, Rep. No. 80, Industrial Health Research Board, London, p. 333, 1937.
4. HANZLIK, P. J., *et al.*: Toxicity, Fate and Excretion of Propylene Glycol and Some Other Glycols, *J. Pharm. and Exp. Ther.*, **67**, 101, 1939.
5. HUNT, R.: Toxicity of Ethylene and Propylene Glycols, *Indust. and Eng. Chem.*, **24**, 361, 836, 1932.
6. JETTER, W. W.: A Critical Survey of Various Chemical Methods for Determining the Alcohol Content of Body Fluids and Tissues, etc., *Quart. J. Stud. on Alcohol*, **2**, 512, 1941-42.
7. KESTEN, H. D., *et al.*: Pathologic Effects of Certain Glycols and Related Compounds, *Arch. Path.*, **27**, 447, 1939.
8. LAUG, E. P., *et al.*: The Toxicology of Some Glycols and Derivatives, *J. Indust. Hyg. and Toxicol.*, **21**, 173, 1939.
9. MULINOS, M. G., *et al.*: The Metabolism and Toxicology of Ethylene Glycol, etc., *Am. J. Pharm.*, **115**, 51, 1943.
10. NEWMAN, H. W.: Acute Alcoholic Intoxication, Stanford Univ. Press, Calif., p. 22, 1941.

SUCCESSFUL COMBINED TREATMENT OF PENICILLIN-RESISTANT GONORRHEA

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RECENT articles have reported spectacular success in the treatment of gonococcic infection with penicillin. In May 1943 Herrell, Cook and Thompson⁵ reported the results of the use of penicillin in the treatment of 3 cases of gonorrhea. Since that time many publications have appeared, particularly those of Keefer and his associates,⁶ Mahoney and others,⁷ Ferguson and Buckholtz,⁴ and Sternberg and Turner,⁸ which have shown that gonorrheal infection responded very rapidly to penicillin treatment. All these observers achieved gratifying results in the treatment of male patients. Cohn, Studdiford and Grunstein¹ studied 44 female gonorrheal patients of whom a total of 43 promptly became bacteriologically negative after treatment with penicillin and remained negative during the follow-up period. In the treatment of a large series of cases the efficacy of penicillin in the sulfonamide-resistant gonococcic infections has been almost complete. Sparse comments have been made on those cases which failed to respond to the usual penicillin treatment. We consider in this report 4 cases which failed to respond to adequate penicillin therapy.

Report of Cases. CASE 1. A married American white soldier, aged 27, was seen on March 20, 1945. He had gonorrhea in 1939 which was adequately and satisfactorily treated. He was sexually exposed on Nov. 2, 1944. He was admitted to hospital at Camp Swift, Texas, on Nov. 13, 1945, with a urethral discharge, smear of which was positive for gonococci. A total of 34 gm. of sulfathiazole was administered in 5 days. This treatment was discontinued on November 17. The next day the urethral smear was still positive for gonococci, in spite of the fact that, in addition to sulfathiazole,

penicillin had also been started on November 15. The patient was given 200,000 units of penicillin intramuscularly on this date. On November 16, 400,000 units were given. Additional penicillin was given on November 18, 19, 20 and 21. A total of 2,600,000 units was administered in this course. Repeated urethral smears continued to show gonococci. Because of this, the patient again was placed on penicillin therapy. From November 27 to 30, 1,600,000 units were given. Urethral smear examinations done on November 27, 28, 29, 30 and 31 were positive for gonococci. On December 9, argyrol instillations were begun and continued until December 22. On December 22, penicillin was again started and continued for a period of 3 days. Argyrol instillation was again given for a period of 3 days following penicillin therapy. This patient was returned to duty on Dec. 28, 1944. Urethral smears performed on December 25, 26 and 27 were negative for gonococci, but his discharge persisted until March 1, 1945, at which time he developed a profuse recurrence. The patient denied any sexual intercourse since Nov. 10, 1944. On March 5, 1945, he was admitted to the Regional Hospital. Repeated urethral smears were positive for gonococci. On March 20 he was transferred to Lawson General Hospital as a sulfonamide and penicillin-resistant case of gonorrhea. Here also positive urethral smears were obtained. Urethral cultures were also positive. Fermentation tests confirmed the presence of the gonococcus. Penicillin assay study *in vitro* failed to show any inhibition. On March 27, April 5 and April 14 he was given fever therapy. After the third fever session the urethral discharge disappeared. Repeated urethral smears and cultures thereafter were negative.

CASE 2. This 23 year old white soldier was inducted into the army in November 1942. He was transferred from Fort Jackson, S. C., Jan. 23, 1945, for the treatment of resistant gonorrhea. This patient stated

that he had sexual intercourse on Oct. 28, 1944. He noticed an acute urethral discharge 8 days following intercourse. A diagnosis of gonorrhea was made Nov. 10, 1944. Repeated urethral smears were positive. On November 10 he was given 100,000 units of penicillin intramuscularly. Urethral smears continued positive. On November 18 he was given 200,000 units of penicillin. This failed to check the discharge and the positive smears. On November 27 he was hospitalized and given 300,000 units of penicillin. Two consecutive urethral smears were negative for gonococcus. He was returned to duty on Dec. 1, 1944. Follow-up examinations were again positive for gonococcus. On December 13 the patient was again hospitalized for urethral discharge. Sulfadiazine was started on December 15 and continued to December 21. A total of 32 gm. was given. The discharge persisted; the urethral smears continued positive for the gonococcus. Follow-up urethral smears continued positive until he was transferred to Lawson General Hospital for fever therapy. Examination at this hospital continued to show a heavy purulent urethral discharge with repeated positive urethral smears and cultures. Identification of the gonococcus was confirmed by sugar studies. During his stay at this hospital he was given 32 gm. of sulfadiazine without any clinical or laboratory improvement. Penicillin assay was performed. No evidence of inhibition *in vitro* was shown.

CASE 3. This 25 year old white soldier was inducted Feb. 24, 1941. He states that early in November 1944 he had illicit sexual intercourse. On Nov. 4, 1944, he noticed a urethral discharge. He was given 100,000 units of penicillin while on duty status. Repeated urethral follow-up smears were positive for gonococci. On Nov. 18, 1945, he was given an additional 200,000 units of penicillin. Urethral smears continued positive. It was necessary to give the patient more treatment. On November 24 he was given 200,000 units of penicillin. Urethral smears were still positive. A heavy urethral discharge persisted. 300,000 units of penicillin were administered on November 28. Follow-up studies demonstrated positive smears. On December 28 sulfadiazine was instituted. A total of 40 gm. were given. The urethral discharge persisted. The smears were positive. The smears continued positive until Jan. 13, 1945. Because this

patient failed to respond to sulfadiazine and penicillin he was transferred to Lawson General Hospital on Jan. 24, 1945. Numerous urethral smears and cultures were found positive for gonococci. Sugar studies were done to confirm the identification of the organism. Penicillin assay *in vitro* was carried out. No inhibition was shown by the cup method used. This patient was given fever therapy and additional 480,000 units of penicillin at the height of the fever. Two sessions of fever were necessary to cure this patient.

CASE 4. This 22 year old colored soldier was inducted July 13, 1944. This patient states that at the time of his induction he had a urethral discharge. According to his story, he first had gonorrhea in 1936 which failed to be completely cured until 1940. During this time he received many forms of treatment. His discharge did not recur until June 1944 prior to his induction. This he believes to be a new gonorrhea, since he had had frequent illicit sexual intercourse. This patient's urethral discharge continued until Aug. 9, 1944, when he was hospitalized and treated for acute gonorrhea. During this hospitalization he was given sulfathiazole, sulfadiazine and a total of 600,000 units of penicillin. The urethral discharge and positive smear continued. On September 28 he again was hospitalized for fracture of the left leg. While receiving treatment for his fractured leg his urethral discharge persisted. On November 6 he was transferred to the venereal ward for further treatment of his gonorrhea. He was given 100,000 units of penicillin. The urethral discharge persisted. The smears continued positive. Beginning on Nov. 17, 1944, he was given 400,000 units of penicillin; no improvement noted. Laboratory studies repeated on numerous occasions were found to be positive for gonococci. This patient was transferred to Lawson General Hospital on Jan. 20, 1945, as a case of penicillin-resistant gonorrhea. The urethral discharge was present and profuse. Repeated urethral smears and cultures were positive for gonococci. Sugar reactions confirmed the identity of the organism. Penicillin assay was performed. This confirmed the clinical findings. No inhibition was demonstrated. Two fever sessions were necessary to cure this case.

Comment. In recent literature thousands of cases of gonorrhea have been treated without encountering instances of penicillin resistance. Sternberg and Turner⁸ in a series of 1686 cases failed to observe any cases of penicillin-resistant gonorrhea. This observation was confirmed *in vitro* by Cohn and Seijo² in which they showed that a 1-10,000 dilution of penicillin killed all the gonococcal strains tested. At this hospital 4 cases were studied by the penicillin assay method. These cases had positive urethral smears and cultures. Fermentation reactions were used to prove the identity of the gonococcus. Penicillin assays showed that the drug had no effect on the growth of gonococci. No inhibition to growth was shown. The method of titration of *N. gonococci* with penicillin (modification of the Oxford method) was as follows: (1) Chocolate blood agar plates containing approximately 25 cc. of agar are seeded with 0.5 cc. of a 24 hour broth culture of *N. gonococci* and allowed to dry for $\frac{1}{2}$ hour. (2) With a sterile glass cylinder a hole was cut in the center of each plate. The bottom of the hole was then sealed with 2 drops of nutrient agar. (3) This cup was filled with 2 drops of penicillin, each drop containing approximately 400 units of the drug. (4) The plates were incubated in CO₂ at 37° C. for 24 and 48 hours. Examinations in all 4 cases failed to show any zone of inhibition. What factors influence the lack of inhibition in these cases have not been determined. Yet, from clinical

and laboratory studies, penicillin failed to cure these patients. Wright⁸ in his discussion of Sternberg and Turner's paper indicated that some patients continued to have a profuse urethral discharge with positive cultures for 6 months or more. The possibility that the excretion of the penicillin in the discharge was a factor in inhibiting the culture growth was ascertained. Two of Wright's patients, both men, had had a profuse discharge for months with positive smears. Yet cultures were negative. Repeated sulfonamide, penicillin and fever treatments failed to alter the discharge or the positive urethral smear findings. A failure rate of 5.2% with penicillin was reported by Dunfield and Mandel⁵ in a series of 154 cases of uncomplicated gonorrhea. This was determined by the presence of discharge, positive urethral smears and cultures.

Summary. Four cases of penicillin-resistant gonorrhea were reviewed. All cases failed to respond to large doses of penicillin. Gonorrhea was proven by urethral smears and cultures. Fermentation reactions were also used. The organisms were shown to be penicillin resistant by *in vitro* studies. Combined sulfonamide-penicillin and/or fever treatments were employed in all of the 4 cases of resistant gonorrhea. All of the cases responded to this form of treatment. Penicillin assays employed by the usual bacteriologic method in 4 cases at this hospital indicate that penicillin-resistant strains of gonococci do exist.

REFERENCES

1. COHN, A., STUDDIFORD, W. E., and GRUNSTEIN, I.: J. Am. Med. Assn., 124, 1124, 1944.
2. COHN, A., and SEIJO, I. H.: J. Am. Med. Assn., 124, 1125, 1944.
3. DUNFIELD, V. M., and MANDEL, A.: New York State J., p. 614, March 15, 1945.
4. FERGUSON, C., and BUCKHOLTZ, M.: J. Am. Med. Assn., 125, 22, 1944.
5. HERRELL, W. E., COOK, E. N., and THOMPSON, L.: J. Am. Med. Assn., 122, 289, 1943.
6. KEEFER, C. S., BLAKE, F. G., MARSHALL, E. K., LOCKWOOD, J. S., and WOOD, W. B., JR.: J. Am. Med. Assn., 122, 1217, 1943.
7. MAHONEY, J. F., FERGUSON, C., BUCKHOLTZ, M., and VAN SLYKE, C.: Am. J. Syph., Gonorr. and Ven. Dis., 27, 525, 1943; Abstr., J. Am. Med. Assn., 123, 862, 1943.
8. STERNBERG, T. H., and TURNER, T. B.: J. Am. Med. Assn., 124, 133, 1944.

MENINGOCOCCUS ENDOCARDITIS

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ALTHOUGH originally described by Weichelsbaum²⁴ in 1887 as the etiologic agent of a specific type of meningitis, the Meningococcus (*Neisseria intracellularis*) is now known to be the etiologic agent not only of one type of meningitis, but also of a generalized septicemia which may be followed by bacterial localization in many different organs, producing a number of clinically distinct and characteristic syndromes. One of these, meningococcic endocarditis, has reached recent prominence as a disease process which may be susceptible to the newer therapeutic agents. However, the fulminating nature of the disease, combined with the difficulties in establishing an early bacteriologic diagnosis, often conspire to delay therapy until the patient's condition is beyond the point of reversibility.

Because of the relative infrequency of primary meningococcic endocarditis, a case will be described in detail, and the natural history of the disease, as derived from 24 cases collected from the available literature, will be discussed.

Case Report. W. B., a 23 year old married gasoline station attendant, entered the Salt Lake General Hospital on January 10, 1945 complaining of weakness, dry cough, weight loss and "heart trouble." The patient had been perfectly well until November 18, 1944, when he developed a severe sore throat and fever. He noticed that lateral, but not anterior-posterior movements of the head produced pain. He went to bed where he remained for 4 to 5 days. The sore throat disappeared, but general aches and pains and malaise supervened, making it impossible for the patient to return to work.

Two weeks after the onset of his illness, he consulted a physician who, after a careful examination, told him he had "bad tonsils" but that he was otherwise normal. He returned home, but because of continued malaise, anorexia, and weight loss, he again con-

sulted his physician 2 weeks later. On this occasion, a low grade fever and a cardiac murmur were found. Because of his continued down-hill course, the patient was told to apply to the hospital for admission. He had observed no rash. There had been no arthralgia, petechiae, or symptoms referable to embolic phenomena. He complained only of a slight dry cough. He had had no stiff neck since the day of onset, and no other symptoms or signs of meningitis. There had been a loss of weight from 158 to 139 pounds since the onset of his illness.

The *past history* revealed that he had had diphtheria at the age of 7 years, but there was no history suggestive of rheumatic infection or impairment of cardiac reserve. He denied any venereal disease and previous blood serology tests for syphilis had been negative. At army induction examinations in February and again in May, 1944, no cardiac disturbance was noted.

The admission examination revealed an acutely and chronically ill, pallid young man who appeared extremely weak but who was in no acute distress. A temperature of 101.6° F. and a pulse rate of 120 per minute were found on admission; the respiratory rate was 28 per minute and the blood pressure 135/20. Except for "freckles" on the shoulders, the skin was negative. Examination of the head and neck revealed no abnormality other than approximately 8 to 10 pea-sized lymph nodes in the anterior and posterior cervical chains bilaterally. The thorax was negative except for the heart, which was enlarged 2 cm. to the right of the midline. The left border of cardiac dullness was percussed at the left mid-clavicular line, and there appeared to be some straightening of this border. A tachycardia was present, but the rhythm was regular. The tones were vigorous, and the precordium heaved moderately. There were no thrills. A loud harsh systolic murmur, heard best at the aortic area, was transmitted to the neck vessels and subclavian arteries bilaterally. A loud, high pitched, early diastolic murmur was heard along the left sternal border. The first and second aortic

sounds were heard clearly. A reduplicated second sound was present at the mitral area, and a loud harsh systolic murmur accompanied by a low pitched diastolic rumble, differing in pitch and intensity from those at the base, were heard at the apex. A Corrigan pulse could be felt in all the peripheral arteries, and Duroziez' sign, as well as capillary pulsation of the nail beds, were also present. Examination of the abdomen was negative, except for a questionably palpable spleen. The remainder of the physical examination was negative.

Blood examination disclosed: erythrocytes, 4.2 million cells per cmm.; hemoglobin, 12.5 gm. %; volume of packed red cells, 32 cc. %; icterus index, 2 units; corrected sedimentation rate (Wintrobe) 35 mm. The total leukocyte count varied from 8000 to 13,400 cells per cmm., and the differential count revealed 6 to 18% juvenile granulocytes, 60 to 70% polymorphonuclears, 0 to 5% eosinophils, 0 to 1% basophils, 12 to 17% lymphocytes and 2 to 8% monocytes.

Urine examinations were negative except for 1+ albuminuria on 1 of 6 determinations, and "occasional" red and white blood cells. A non-hemolytic staphylococcus, and a pneumococcus were cultured from the throat. Urine cultures and prostatic smears and cultures were negative. Three of 6 venous blood cultures revealed a gram-negative diplococcus. One arterial blood culture was negative, but one culture of sternal marrow yielded a better growth of the same gram negative organism than did the cultures of venous blood. It is noteworthy that these cultures did not become positive until 7 to 9 days after the blood had been drawn. Because these organisms fermented maltose and dextrose with the production of acid, but did not ferment levulose, they were classified with the *N. intracellularis* group. No typing sera were available.

Roentgenograms of the chest revealed nothing of note. The heart size and contour were normal. The transverse cardiac diameter was 13.3 cm. and the transverse intrathoracic diameter was 31 cm. The electrocardiogram revealed a heart rate of 100 beats per minute with a P-R interval of 0.16 sec. and QRS of 0.08 sec. T wave inversion was noted in Lead I on admission. This became more marked during the course of the illness. Serial chest leads were in no way remarkable

except as they demonstrated inverted T waves over the left ventricle.

The hospital course of this patient was, at first, uneventful except for the continuous spiking fever which was often of the "double quotidian type" (see Fig. 1). Weakness and debility increased progressively. On January 23, 1945, 15 days after admission, the first positive blood culture was reported and penicillin was begun. An initial dose of 20,000 units was given intravenously and this was followed by 20,000 units intramuscularly every 3 hours.

During the evening of the same day, the patient complained of general abdominal pain and inability to void. On the following morning, catheterization was performed, but the bladder was empty. Abdominal distress was marked and an indefinite tender mass was palpable in the right upper quadrant. The abdomen was distended with gas and bubbling râles could be heard in the posterior chest. For the first time, ecchymoses appeared on the right foot. Within a few hours, the liver was palpable 5 finger breadths below the costal margin, and numerous loud coarse râles could be heard throughout the chest. The venous pressure was 250 mm. of water. The blood urea nitrogen at this time was found to be 34.7 mg. per 100 cc.; the plasma chloride, 433 mg., and the CO₂ combining power 19 vol. %. The electrocardiogram revealed a P-R interval of 0.16 sec. with widening of the QRS complex to 0.16 sec. The heart rate at this time was 110 beats per minute. Serial precordial leads demonstrated changes compatible with a uniform depression of myocardial conductivity. Despite sedation, parenteral ouabain, aminophylline, bloodless phlebotomy, and nasal oxygen, the patient failed rapidly and died within a few hours.

Autopsy (2 hours after death) yielded the following positive findings on gross and histologic examination:

Gross examination of the heart revealed a normal epicardium and myocardium. There was a massive fresh thrombo-ulcerative endocarditis of the left anterior aortic valve cusp, which had ulcerated through the septum and protruded into the left atrium as a mural thrombus just above the mitral valve. This latter valve showed only a minimal vegetative process on the medial cusp. There was no evidence of pre-existing valvular deformities. On histologic examination, the myo-

cardium showed moderately advanced parenchymatous degeneration and areas of leukocytic infiltration suggesting acute focal myocarditis. No Aschoff bodies were found.

Multiple small and large hemorrhages were noted throughout the *peritoneum*. There was a fibrinopurulent peritonitis, and bilateral hydrothorax, hydropericardium, ascites and anasarca. The *kidneys* showed healed infarcts of various sizes and ages, parenchymatous degeneration and passive congestion. Focal (embolic) subacute glomerulonephritis was also present. There was congestion of the *liver* and congestion and edema of the *lungs*. The *spleen* weighed 450 gm. and showed anemic infarcts and diffuse hyperplasia.

Permission was not granted for examination of the central nervous system.

Incidence. The incidence of meningococcic endocarditis, as compared with other types of endocarditis, appears extremely low in most statistical studies. Thayer³² described 198 cases of acute bacterial endocarditis in Baltimore, Williams³⁸ 38 cases in Nashville, Lenhartz²¹ in Germany and Horder¹⁴ in England, 134 additional cases, and Clawson⁴ collected 46 cases—a total of 416 cases all together in which bacteriologic studies were done. None of these instances of endocarditis were attributed to the meningococcus. The gonococcus was described in 2 to 12 % of cases in the various series. Harbitz⁹ found that 2 out of 32 of his cases of acute bacterial endocarditis were due to a “gram negative” diplococcus, but he did not further identify the organism. Dauphinee⁶ reviewing 304 cases of endocarditis, stated that the meningococcus is “only rarely” the etiologic agent.

However, White³⁷ stated that in a group of 48 cases of acute bacterial endocarditis in Boston, 4 were caused by the meningococcus and an equal number by the gonococcus. Because of this study and also because of the comparative frequency of recent isolated reports of meningococcic endocarditis in the literature, we suspect that the incidence of primary acute bacterial endocarditis caused by the meningococcus is higher than has been hitherto found. There is evidence to suggest that

the earlier authors did not differentiate clearly between the gonococcus and the meningococcus, which may account for the scarcity of reports of meningococcic endocarditis in the older literature.

Herrick¹³ was the first to describe the usual course of meningococcic sepsis, which he found to occur in 3 stages. The first, lasting 2 days to 6 weeks, is a local inflammation of the upper respiratory passages. This is followed by a bacteremia lasting approximately 48 hours, after which the bacteria localize in the meninges, the heart, or at other sites throughout the body. This “average” picture is subject, however, to infinite variation in length and order of stages, or the disease may terminate at any stage without progressing further.

Thus we find that endocarditis can occur as a complication of meningitis, as a complication of meningococcic septicemia, or as a “primary” disease entity. Endocarditis was found to be a complication of meningococcic meningitis in 6 % of Smithburn’s cases,²⁹ but was not mentioned as a complication in a series of 4464 cases reported by Horowitz and Perroni.¹⁶ In the Army during the first World War, endocarditis was found by Krumbhaar and Cloud¹⁹ in 3 cases all of which also showed signs of meningitis. Approximately half of the cases of meningococcic endocarditis have followed meningitis.²² In 12 to 27 % of cases of recognized chronic meningococcic septicemia endocarditis has developed.^{1,2,26} It is difficult to determine accurately the proportion of cases of endocarditis that are preceded by a simple, comparatively long-standing meningococcic septicemia, although a history suggestive of preceding septicemia of 2 or more weeks’ duration was found in 5 of 11 of this series.

Pathology and Pathogenesis. In contradistinction to the more familiar streptococcus viridans endocarditis, meningococcic endocarditis usually develops upon previously undamaged heart valves. In only 3 of 19 autopsied cases reported in the literature cited here was there evidence of old chronic valvular disease in addition to the acute valvulitis. In another report¹⁷

no mention is made of the possible presence of luetic aortitis in addition to the acute aortic valvulitis, although the patient's Wassermann was recorded as 3 plus. In an additional 7 cases that were not autopsied, there was no history of previous rheumatic fever or heart disease.

Like *Streptococcus viridans* endocarditis, meningococcic endocarditis usually involves the left side of the heart. Of 26 autopsied cases, the mitral valve alone was involved in 17, the aortic in 3, both aortic and mitral in 5, and aortic and tricuspid in one. Pericarditis was also described in 3 and myocarditis in 9 out of 18 of these cases. Meningococcic myocarditis, according to Saphir,²⁸ is characterized by a hemorrhagic exudate, and destruction of muscle fibers, accompanied by the early appearance of endothelial leukocytes and the finding of gram negative intracellular diplococci. In later stages, foci of necrosis, such as are found in subacute *Strep. viridans* endocarditis, appear.

The pathogenesis of meningococcic endocarditis in previously undamaged hearts, has been studied by Miller²⁵ in horses. In these animals, he described an initial endothelial edema which gave rise to a separation of the endothelial layer from the subendothelial tissue. This produced a wrinkling, fragmentation, and desquamation of the endothelium. Gram negative diplococci were found on the surface and within these desquamating areas. On some valves, fibrin layers containing endothelial cells, blood elements and bacteria, and on others early reparative growths of fibroblasts and endothelial buds could be seen. These changes progressed through stages leading to that also described in human autopsy material, where the typical finding is that of a friable thrombotic vegetative process protruding from the surface of a valve that also shows acute ulcerative and productive inflammatory changes.

Miller²⁵ suggested that these early endothelial changes may be the result of an "alteration in the course of immunization" which produces an endothelium "more vulnerable to the toxic products" of the men-

ingococcus. These toxic products, then, prepare the way for actual colonization on the valve surface. He showed that the bacteria probably do not enter through end-arteries in the valve, but rather, localize on the surface of the damaged endothelium. His theory of a primary toxic endothelial damage was supported by the finding of similar endothelial changes in arteries of the lung and other organs.

Clinical Picture. In 24 cases, 17 were males and 6 females. Except for 1 Negro all of the cases were in the white race. One patient was 13 years old, 7 ranged between the ages of 15 and 25, 6 between 25 and 35, 4 between 35 and 45, and 3 were over 45 years of age.

Three modes of onset of primary meningococcic endocarditis can be distinguished. Infrequently (2 of this series) the patient, previously perfectly well, is overcome with symptoms and signs of acute heart failure: dyspnea, orthopnea, cough productive of pink foamy sputum, dullness and bubbling râles in the chest, a dilated heart with rapid pulse and heaving precordium, a large tender liver, peripheral edema and cyanosis.

In other cases (11 of this series) the onset is that of an acute septicemia with chills, high temperature and marked prostration. Finally, as in 11 of this series, the onset may be subacute. In these, the patient characteristically believes that he has "the flu," but instead of recovering rapidly, his anorexia, malaise, fatigue, and weakness continue and progress until within weeks or months he appears before the physician, a chronically ill and prostrated individual. A 4th mode of onset of endocarditis, in which the cardiac involvement follows a definite meningococcic meningitis, will not be discussed here since the diagnostic problem can be quickly solved by careful neurologic examination together with a microscopic examination of the spinal fluid.

Certain symptoms and signs are of clinical significance in the diagnosis of meningococcic endocarditis, but do not dis-

tinguish it from simple meningococcic septicemia (Fig. 1).

The arthralgia, which was present in half the cases of this series, is characterized by its mildness. Joints most often involved are knees, ankles, elbows and

days or weeks in the early course of the disease and does not recur.

The rash, which occurred in approximately half of these cases, is extremely variable in its appearance. Occasionally a macular rash is present that resembles the

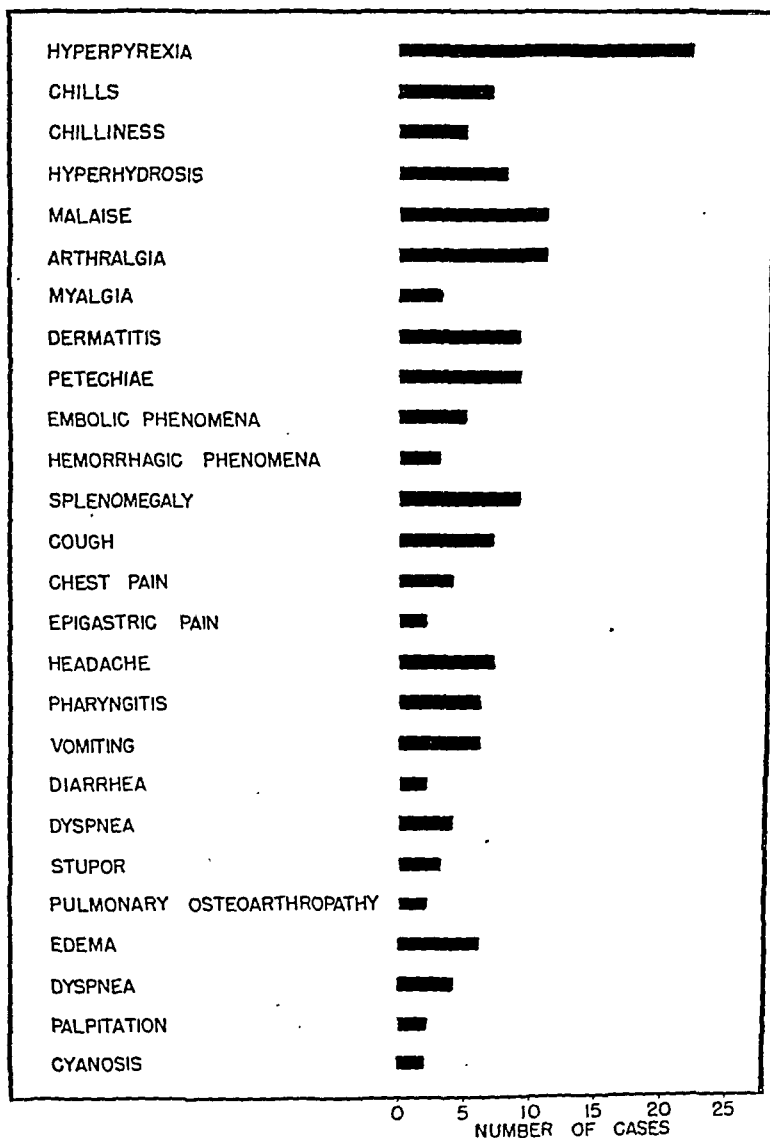


FIG. 1.—The frequency of certain symptoms and signs in 22 cases of meningococcic endocarditis.

wrists. Usually pain and tenderness alone are present, but occasionally objective findings of acute arthritis—heat, swelling, redness and fluctuation—are found in some degree. Roentgenographic evidence of joint changes has not been described. This arthralgia is usually present for only a few

rose spots of typhoid fever. The rash may be papular or pustular in character. On occasion it has been compared to that of secondary syphilis and in other cases it has resembled erythema multiforme or erythema nodosum. In many cases, a petechial or purpuric eruption is present

alone or in addition to one of the other forms. The duration and extent of the rash are as variable as the morphology itself, and it may occur at any time during the course of the disease.

Other commonly found symptoms and signs are malaise, anorexia, headache, nausea and vomiting, muscular aches and pains, chilliness or true chills, night sweats, cough and pharyngitis, such as one might expect in any severe bacterial systemic disease. The spleen was palpable in $\frac{1}{3}$ of the cases in this series.

Another set of symptoms and signs, no one of which was present in more than 20% of this series before the terminal stage, suggested cardiac involvement. These included embolic phenomena (other than petechiæ), chest pain, osteoarthropathy, Osler's nodes, palpitation, cyanosis, peripheral edema, dyspnea and cardiac dilatation.

Hennell¹² and Carbonell² have commented on the frequency with which a diagnosis of malaria has been made in these cases because of this type of temperature curve. Often the same patient may show different types of temperature curves during different stages of the disease.

Our case demonstrated a 4th type of temperature curve (Fig. 2) which has not previously been described in meningococcic infections, although it can be seen in the temperature graph of the patient reported by Willis³⁹ (Fig. 3). This type of fever has been described in gonococcus endocarditis by Horder and Gow,¹⁴ by Williams³⁸ and under the title of the "double quotidian" fever of gonococcus endocarditis by Fletcher.⁷ As the name would imply, this fever is characterized by two distinct peaks occurring each day in the temperature curve. Our patient demonstrated this phenomenon on 6 of the 15

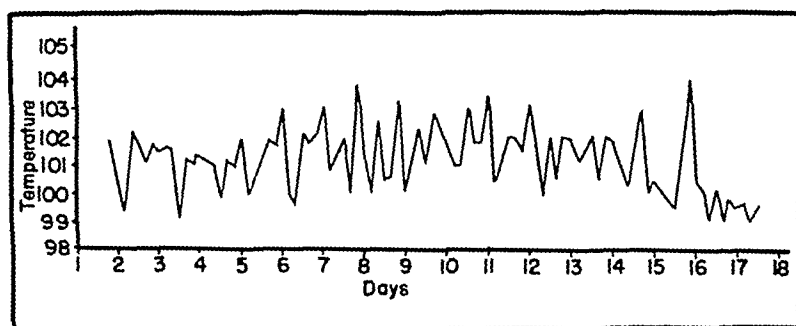


FIG. 2.—Temperature chart of Patient W. B.

In addition, the usual physical signs of involvement of the specific valves were present in all but 1 case at some time during the course of the disease.

Many different types of febrile reaction have been described in meningococcic endocarditis. Occasionally there is a chronic low-grade fever that undulates up and down at irregular intervals. Usually it is a definite spiking type of curve with elevations to 103 to 105° F. each evening, and subsiding to normal by the following morning. Frequently a normal or slightly elevated temperature will be interrupted every 2d, 3d or 4th evening by chills and spiking temperature to 103 to 105°. Both

days during which he was observed. It can no longer be said, then, that this type of fever is characteristic only of endocarditis due to *N. gonorrhææ*. The clinician is, therefore, advised, when he encounters this "double quotidian" fever in a case of endocarditis, to search diligently for both *N. gonorrhææ* and *N. intracellularis*.

The laboratory findings in cases of meningococcic endocarditis are similar to those encountered in any of the bacterial endocardidities. Erythrocyte count, hemoglobin, and hematocrit, show a variation from the normal to a profound anemia which is usually of the normocytic type. Some degree of anemia was found in 12 of 16

cases in this series, and the anemia usually increased with the severity and prolongation of the disease.

The leukocyte count varied from normal values to counts as high as 28,000 per cmm., with a differential often, but not always, showing a marked "shift to the left." In the cases cited in this report leukocytosis was recorded in 17 of 22 cases during some part of the illness. As in other severe infections the more toxic cases in this series often showed a marked "shift to the left" in the differential count without any increase in the total number of leukocytes. The erythrocyte sedimentation rate is usually elevated in this disease. In some cases, albuminuria and microscopic hematuria and pyuria have

generous amounts on warm moist slants of the enriched media. Although venous blood is usually adequate for culture, we have found, as was suggested by Horowitz and Perroni¹⁶ that cultures of sternal marrow appear to yield more colonies per volume than are obtained from simultaneous venous puncture. One arterial blood culture was of no greater value than venous blood, in our hands.

Differential Diagnosis. Because of the almost universal presence of a significant cardiac murmur in cases of acute endocarditis, it is usually not difficult to distinguish disease of this category from cases falling in the vast group of "fever of unknown origin." The clinical picture of meningococcic endocarditis is not suffi-

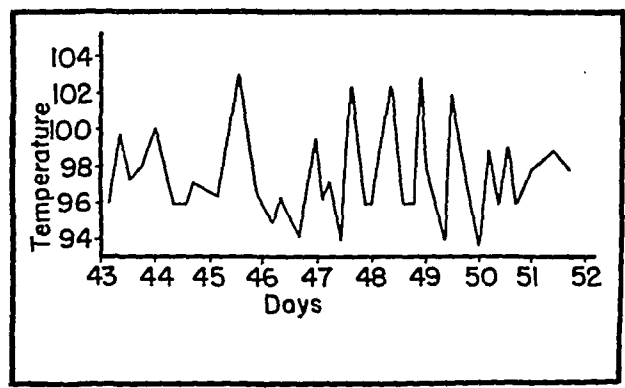


FIG. 3.—Temperature chart reported by Willius.³⁹

been recorded. These are usually slight and result, apparently, from renal infarction or from focal embolic nephritis.

Roentgenograms of the heart reveal changes due to dilatation of the various chambers, and the electrocardiogram often records changes in pattern of a non-specific type.

Blood cultures were positive for the meningococcus in all 24 cases cited. It must be emphasized that this organism can be grown only with difficulty and on enriched media such as blood or chocolate agar and in an atmosphere of increased carbon dioxide tension. Since it is very sensitive to light, cold, and desiccation, material for culture should be kept warm and cultured as soon as possible and in

sufficiently clear cut so that it can be distinguished with certainty from the other varieties of acute endocarditis. However, there are 3 characteristic signs and symptoms which, when present, make one suspicious of this diagnosis, and which tend to rule out other etiologic agents. These are the presence of skin lesions, arthralgia, and a tertian, quartan, or double quotidian temperature curve. The absence of previous valvular damage and the absence of pneumonia, abscess or other local infections tends to rule out certain other types of acute endocarditis.

Endocarditis due to the pneumococcus in the preponderant majority of cases is a complication of pneumococcic pneumonia or some other local pneumococcic infec-

tion.^{32,33} Arthralgia and skin lesions, other than those due to petechiæ, are rarely encountered, and the disease is usually more fulminating than that caused by the meningococcus.

In staphylococcic endocarditis, Thayer³² found pre-existing valvular disease in approximately half the cases, in contrast to the pre-existence of valvular disease in only 13 % of the cases due to the meningococcus reported in this series. In $\frac{2}{3}$ of the cases the endocarditis was a complication of a previously recognized staphylococcic infection and usually pyemia was present. Arthritis was found in 24 % of the patients, but none had any rash other than petechiæ.

Gonorrheal endocarditis presents the most difficult differential diagnosis, since in most cases no portal of entry of the bacteria is evident, since about $\frac{1}{3}$ of cases demonstrate an arthritis, and since the course and temperature curves resemble those of meningococcic endocarditis very closely.³² The statistically greater incidence of this disease in the colored race and the usual absence of any true skin rash, are perhaps the only methods of distinguishing the 2 diseases other than by bacteriologic studies.

In acute endocarditis due to a streptococcus (usually β -hemolytic streptococcus³²) a definite portal of entry was found in about 60 % of cases. About $\frac{1}{4}$ of the patients complained of arthritis, but none had a significant rash. About 60 % of these acute cases represented infection superimposed on previously damaged valves.

Course, Prognosis and Treatment. The course of meningococcic endocarditis is usually acute and may be fulminating. The duration in 16 of 21 cases in this group was less than 9 weeks. The shortest course was 10 days and the longest over 8 months. Unless specific treatment is instituted, the patient fails steadily until

death ensues from the toxemia, from heart failure, or from embolic phenomena.

Most authors state that the prognosis is very poor; but Swift³¹ finds that the outlook in this disease is better than in most bacterial endocardidities. In the series reported here, recoveries were reported in 5^{6,20,23} of 23 cases, although in 2 of these the diagnosis may be questioned, and in none was the follow-up sufficiently long to rule out recurrences. Antiserum alone was given in 3 of these recovered cases;²³ antiserum, hyperthermia, and prontosil were used in the 4th;²⁰ and sulfanilamide, sulfapyridine, and sulfathiazole in the 5th.⁵ Other authors have used all combinations of antiserum, transfusions, sulfonamides, hyperthermia and penicillin, with no remarkable results. Penicillin, has, thus far, not been found to be as effective against other infections due to the meningococcus as are the sulfonamides, but because of the serious nature of endocarditis, a full combined therapeutic course of penicillin, sulfonamide, and antisera should probably be given in all cases of this disease. Anticoagulants have not been tried in any cases of this series. Their value in the treatment of other types of endocarditis is still in dispute.¹⁸

Summary. One hitherto unreported case of primary meningococcic endocarditis, together with 24 others collected from the literature, have been presented. It is stated that in many cases the clinical picture is quite characteristic of this bacteriologically specific type of acute endocarditis; so much so that one may often obtain, in individual cases, a definite clue as to the etiologic diagnosis. Most characteristic in the clinical picture of meningococcic endocarditis, are the presence of skin lesions, arthralgia, and a tertian, quartan or double quotidian type of temperature curve, together with the symptoms and signs of acute septicemia and physical signs of cardiac valvular involvement.

REFERENCES

1. APPELBAUM, E.: Chronic Meningococcus Septicemia, *Am. J. Med. Sci.*, **193**, 96, 1937 (quoted by Nye and Semish²⁶).
2. CARBONELL, A., and CAMBELL, E. P.: Prolonged Meningococcemia, *Arch. Int. Med.*, **61**, 646, 1938.
3. CECIL, R. L., and SOPER, W. B.: Meningococcus Endocarditis With Septicemia, *Arch. Int. Med.*, **8**, 1, 1911.
4. CLAWSON, B. J.: Endocarditis, With Special Reference to Subacute Bacterial Type, *Arch. Int. Med.*, **33**, 157, 1924.
5. CUTTS, J. G., KRAFT, G., and WILCOX, P. H.: Meningococcic Endocarditis, *Lancet*, **1**, 292, 1942.
6. DAUPHINEE, J. A.: Bacterial Endocarditis, *Univ. Toronto Med. J.*, **8**, 131, 1931.
7. FUTCHER, P. H.: Double Quotidian Temperature Curve of Gonococcal Endocarditis, *Am. J. Med. Sci.*, **199**, 23, 1940.
8. GWYN, N. B.: Subacute Meningococcal Endocarditis, *Arch. Int. Med.*, **48**, 1110, 1931.
9. HARBITZ, F.: Studien über Endokarditis, *Deutsch. med. Wchnschr.*, **25**, 121, 1899.
10. HARTWELL, R. M.: Meningococcic Endocarditis and Myocarditis, *Am. J. Dis. Child.*, **58**, 823, 1939.
11. HEINLE, R. W.: Meningococcic Septicemia, Report of 5 New Cases, *Arch. Int. Med.*, **63**, 575, 1939.
12. HENNEL, H., and WIENER, H. J.: Report of Case of Chronic Meningococcemia, *Med. J. and Rec.*, **131**, 292, 1930.
13. HERRICK, W. W.: Extrameningeal Meningococcus Infections, *Arch. Int. Med.*, **23**, 409, 1919.
14. HORDER, T., and GOW, A. E.: Essentials of Medical Diagnosis, Baltimore, Wood, 1930 (quoted by Williams³⁹).
15. HORDER, T. J.: Infective Endocarditis, *Quart. J. Med.*, Oxford, **2**, 289, 1908-1909 (quoted by Williams³⁹).
16. HOROWITZ, A., and PERRONI, J.: Meningococcic Meningitis in Santiago, Chile, 1941-1943, *Arch. Int. Med.*, **74**, 365, 1944.
17. HYLAND, C. M.: Meningococcus Endocarditis, *J. Am. Med. Assn.*, **92**, 1412, 1929.
18. KELSON, S. R.: Observations on Treatment of Subacute Bacterial Endocarditis Since 1939, *Ann. Int. Med.*, **22**, 75, 1945.
19. KRUMBHAAR, E. B., and CLOUD, J. H.: Acute Meningococcic Endocarditis and Septicemia, *J. Am. Med. Assn.*, **71**, 2144, 1918.
20. KRUSEN, F. H., and ELKINS, E. C.: Fever Therapy for Gonococcemia and Meningococcemia With Associated Endocarditis, *Proc. Staff Meet. Mayo Clin.*, **12**, 324, 1937.
21. LENHARTZ, H.: Über die septische Endokarditis, *München. med. Wchnschr.*, **48**, 1123, 1901.
22. MACMAHON, H. E., and BURKHARDT, E. A.: Meningococcus Endocarditis: Report of a Case, *Am. J. Path.*, **5**, 197, 1929.
23. MASTER, A. M.: Meningococcemia With Endocarditis, *J. Am. Med. Assn.*, **96**, 164, 1931.
24. MELNOTTE, P., and FORTE, P.: Endocardite maligne aigue à meningocoque A, *Bull. et mém. Soc. méd. d. hôp. de Paris*, **48**, 1219, 1932.
25. MILLER, J. K.: Meningococcal Endocarditis in Immunized Horses, *Am. J. Path.*, **20**, 269, 1944.
26. NYE, R. B., SEMISCH, C. W., and MERVES, L.: Chronic Meningococcemia, Complicated by Acute Endocarditis, *Ann. Int. Med.*, **16**, 1245, 1942.
27. RHOADS, C. P.: Vegetative Endocarditis Due to Meningococcus, With Case Report, *Am. J. Path.*, **3**, 623, 1927.
28. SAPHIR, O.: Meningococcus Myocarditis, *Am. J. Path.*, **12**, 677, 1936.
29. SMITHBURN, K. C., KEMPF, G. F., ZERFAS, L. G., and GILMAN, L. H.: Meningococcic Meningitis, Clinical Study of 144 Epidemic Cases, *J. Am. Med. Assn.*, **95**, 776, 1930.
30. STEVENSON, W. D. H.: Case of Chronic Meningococcic Septicemia With Bacterial Endocarditis, *Brit. Med. J.*, **2**, 1173, 1931.
31. SWIFT, H. F.: Nelson's Loose-leaf Living Medicine, New York, Nelson, **4**, 332, 1926.
32. THAYER, W. S.: Studies on Bacterial Endocarditis, *Johns Hopkins Hosp. Rep.*, vol. **22**, Fasc. 1, 1926.
33. TINSLEY, C. M.: Pneumococcic Endocarditis, *Arch. Int. Med.*, **75**, 82, 1945.
34. WEICHELBAUM, A.: Quoted by Stitt, E. R., Clough, P. W., and Clough, M. C., *Practical Bacteriology, Hematology, and Animal Parasitology*, 9th ed., Philadelphia, Blakiston, 1938.
35. WEINDEL, R.: Über Meningokokkensepsis und Endokarditis, *Klin. Wchnschr.*, **13**, 338, 1934.
36. WHILLANS, M. G.: Meningococcus Endocarditis and Myocarditis, *Am. J. Path.*, **16**, 365, 1940.
37. WHITE, P. D.: Heart Disease, 3rd ed., New York, Macmillan, 1944.
38. WILLIAMS, R. H.: Gonococcic Endocarditis, *Arch. Int. Med.*, **61**, 26, 1938.
39. WILLIUS, F. A., and EATON, L. M.: Clinic on Meningococcemia With Vegetative Mitral Endocarditis, *Proc. Staff Meet. Mayo Clin.*, **12**, 762, 1937.

AZOTEMIA IN GASTRO-INTESTINAL BLEEDING

THE INGESTION OF SHED BLOOD IN HUMANS.

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THE past decade has seen numerous workers drawn to the problem of azotemia resulting from gastro-intestinal hemorrhage. Black,¹ in his critical review of the subject, came to the conclusion that "the available evidence suggests that the usual moderate rise in blood urea is accounted for mainly by absorption of nitrogen in large amounts from the blood in the bowel when the kidneys are hampered by a diminished volume—flow of blood." Schiff and his co-workers,^{5,6} on the other hand, were convinced from their observations on 53 cases, that the azotemia was previously due to absorption of blood proteins from the intestinal tract. Yuile and Hawkins⁷ fed mongrel dogs blood fractions, such as, hemoglobin, and plasma proteins, and arrived at the same conclusions that Schiff did. Unfortunately, Yuile and Hawkins failed to bleed their animals before feeding blood components. This experimental work does not parallel the actual conditions occurring in individuals who bleed into their gastro-intestinal tract. Kaump and Parsons³ simulated human gastro-intestinal bleeding in experimental animals. They bled dogs from the heart and fed the animals their own blood. They concluded that much remained to be clarified, although they were inclined to agree with Schiff that the azotemia was due largely to absorption of the protein (blood) from the intestines. Johnson² stated that the azotemia of gastric hemorrhage did not occur in patients in the absence of reduction in renal function.

It may be mentioned that Yuile and Hawkins found that the time required to reach the maximum blood urea N in mongrels was about $4\frac{1}{2}$ to 10 hours after blood feedings. Kaump and Parsons ob-

served the maximum rise to be about 24 hours. This approximated more closely the findings of Black and Schiff, *et al.* in human gastro-intestinal bleeding.

It was our purpose to attempt to correlate the different conclusions of these workers, and, if possible, to present experimental work nearly approaching the physiologic conditions existing in man by using human subjects. How much blood must be lost in the intestines to produce a significant azotemia in man? Does the question of a renal factor based on diminished volume flow enter into the picture, as propounded by Black—or is the phenomenon primarily one of alimentary azotemia? These were the questions to be answered.

Experimental. A. The authors and 3 of their medical corps associates acted as subjects. All were in normal health and under 40 years of age. Three to 5 days prior to the experiment, urea N, plasma proteins, phenols, hematocrit index, creatinine and uric acid determinations were performed on specimens of their blood. Routine urinalysis including microscopic examination, and a urea clearance test were carried out at the same time. The values obtained were all normal. Without any breakfast, and after a 10 hour fast, the men were bled to the amount of 580 cc. in 25 cc. of 5% sodium citrate solution. A venepuncture just prior to the large bleeding provided the necessary blood for repeating the above chemical studies. A few minutes after withdrawing the 580 cc. of blood, the subjects drank their own blood followed by 100 cc. of water. The ingestion was spread over a period of 30 minutes. Urea clearance, blood urea N, creatinine, blood phenols, and uric acid determinations were done every 3 hours for 12 hours following the ingestion of blood. The subjects were permitted an occasional peppermint candy, water, and smoke throughout this

12 hour period. They maintained their usual daily activities. A number of urinalyses during the experiment showed no abnormal elements in any of the specimens.

The psychic trauma was non-existent. Two officers complained of a taste of liver about 3 hours after feeding. No nausea, vomiting or diarrhea was reported. At the completion of the 12 hour period, a light supper was eaten, and no other food was ingested that night. The following morning, without breakfast (24 hours after blood ingestion), a complete repeat chemical examination of the blood was performed on each subject, plus a urea clearance test. Three hours later the same studies were again

tein ingestion. The hematocrit index fell slightly, as was expected. The moderate increase in uric acid (Fig. 2) could be explained on the basis of the existence of nucleoproteins and uric acid itself in the whole blood. The fall in plasma proteins needs no discussion. The increase in phenols was probably due to the presence of phenolic-amino acids in the blood proteins. The urea clearance values in Figure 3 indicate a complete normal range for the group. However, one member showed a 68% of average normal function at the 6½-hour mark. His previous clearances as

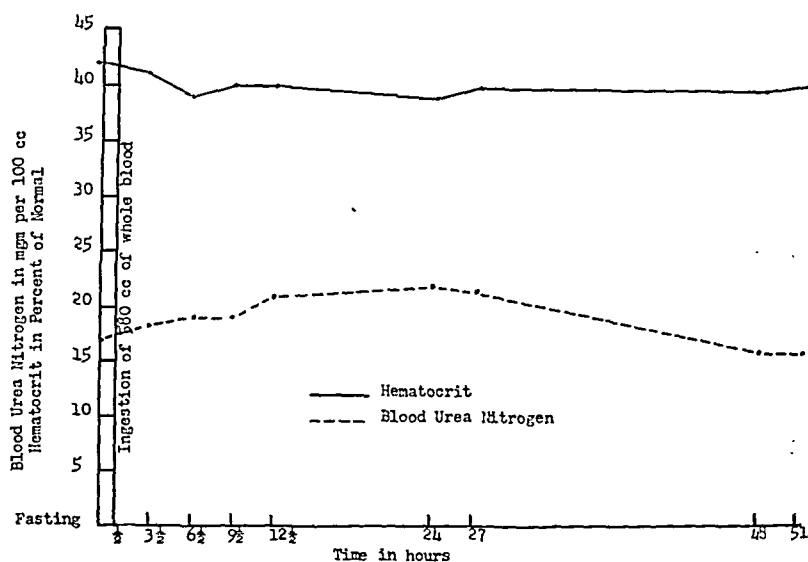


FIG. 1.—Blood urea nitrogen and hematocrit readings following the autoingestion of 580 cc. of whole blood. (Average values of 5 subjects.)

repeated. The usual lunch and supper were then permitted. Repeat blood and urine studies were performed 48 and 51 hours after the blood ingestion. Since little variation was encountered in the values obtained between subjects, they were averaged and the results appear in Figures 1, 2 and 3. Interestingly, during the experimental period only one subject had one loose tarry stool—all the others had black, formed stools throughout the investigation.

It is apparent from Figure 1 that the expected high elevation in blood urea N did not occur. The average maximum increase was small and could be accounted for by the ordinary rise due to large pro-

well as those following were within normal limits.

If one considers the amount of protein ingested in 580 cc. of whole blood, it is easily over 100 gm. of protein. This is more than the average adult eats in 24 hours.

There was the possibility that insufficient blood may have been removed to produce systemic effects similar to those observed in patients with massive hemorrhage into the gastro-intestinal tract. Three more medical officers, therefore, volunteered to donate 800 cc. of blood and undergo the studies carried out in A.

B. Blood ingestion, time intervals, chemical and microscopic examinations of the urine as well as chemical studies of the blood were carried out in exactly the same

the day. It was no longer present the following morning. All subjects showed tarry stools within $3\frac{1}{2}$ hours after the blood ingestion. One individual passed 4 stools in

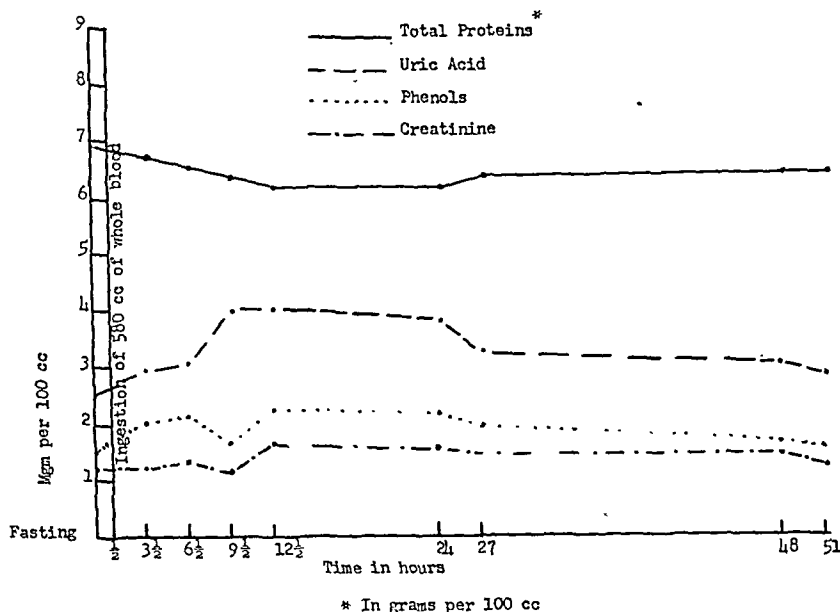


FIG. 2.—Blood total proteins,* uric acid, phenols and creatinine following the autoingestion of 580 cc. of whole blood. (Average values of 5 subjects.)

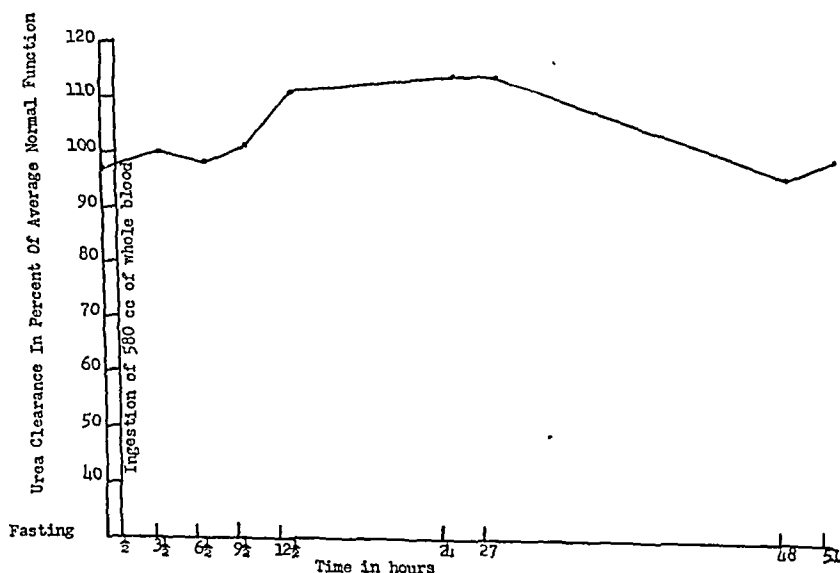


FIG. 3.—Urea clearance after autoingestion of 580 cc. of whole blood. (Average values of 5 subjects.)

manner as in A except for the larger blood donation and ingestion. The subjects complained of vertigo and were pale. This restricted their normal activities to a minimum. The vertigo persisted throughout

a 14 hour period after the blood ingestion. The other 2 passed 3 tarry stools in the same interval. Within 32 hours all 3 subjects were passing black formed feces. The officer who had 4 bowel movements in 14

hours continued to have a tarry stool at the 24 hour period. This could be termed a diarrhea, because none of the men habitually had more than 2 bowel movements a day.

protein, and very slight rise in creatinine. Because the individual variations were not significant, the results were averaged. Although the quantitative difference in blood loss was only 220 cc. between Groups

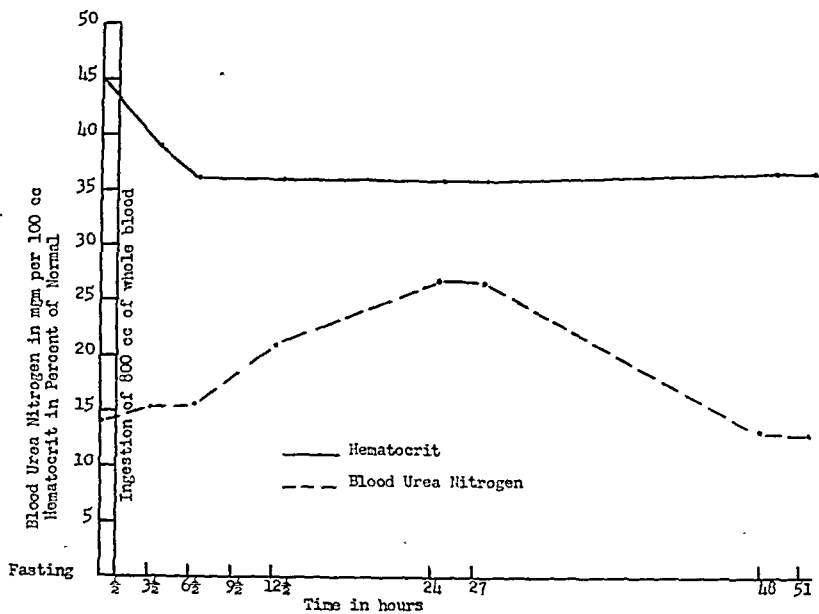


FIG. 4.—Blood urea nitrogen and hematocrit readings following the autoingestion of 800 cc. of whole blood. (Average values of 3 subjects.)

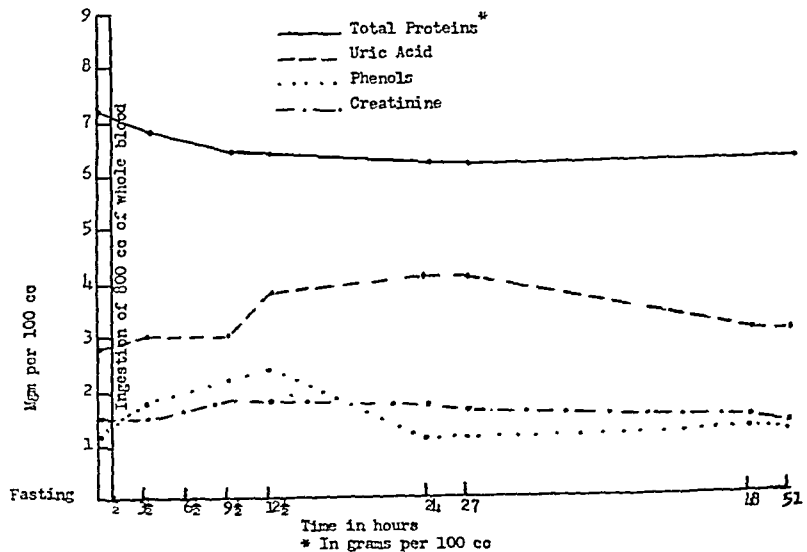


FIG. 5.—Blood total proteins,* uric acid, phenols and creatinine following the autoingestion of 800 cc. of whole blood. (Average values of 3 subjects.)

The findings in Figures 4, 5 and 6 show a definite azotemia, reduced urea clearance, fall in hematocrit index, rise in blood phenols and uric acid, fall in total

A and B, it appears that enough blood has been lost at the 800 cc. level to produce a picture similar to the azotemia in gastro-intestinal bleeding. The marked difference

in urea nitrogen figures and urea clearance findings in both groups is an indication of the disturbance established in renal function of the blood loss. The other values obtained for blood proteins, hematocrit index, uric acid, and blood phenols are not unexpected and do not vary much from those observed in Group A.

The maximum rise in blood urea N figures was observed to occur in both groups at 24 to 27 hours after the blood ingestion. This agrees with the results of Black and of Schiff, *et al.*

and particularly in urea clearance. To test this, another individual was fed a large beefsteak, the protein content of which was calculated at 159 gm., immediately after donating 500 cc. of blood for a transfusion. Certain technical difficulties arose making it impossible to obtain blood and urine specimens at the same intervals as in the previous experiments. We did manage to compare the fasting urea clearance and blood urea N before blood was withdrawn for the transfusion with those obtained 24 and 30 hours after the beef protein was

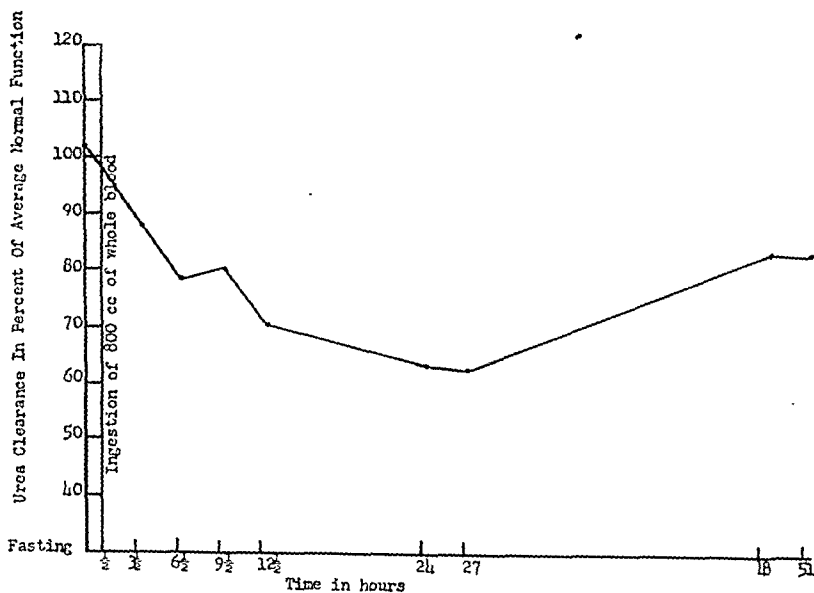


FIG. 6.—Urea clearance after autoingestion of 800 cc. of whole blood. (Average values of 3 subjects.)

Discussion. In the 3 subjects studied in Group B, a loss of 800 cc. of whole blood from the vascular system into the gastro-intestinal tract produced definite metabolic changes. On the other hand, no such picture occurred in the 5 cases in Group A where 580 cc. of blood was lost into the stomach. It appears that a critical level exists between the 580 cc. and the 800 cc. blood loss. A point seems to be reached in circulating fluid dynamics where interference with renal function becomes manifest. We make this statement because we cannot conceive of 40 to 50 gm. increase in protein intake (based on the 220 cc. of increased blood ingested) causing such a marked change in blood urea nitrogen,

eaten. The urea N rose to 22.3 mg./100 cc. from a fasting level of 16.1 mg./100 cc. The subject did not eat anything for 24 hours after the beefsteak was eaten. The blood urea clearance remained within normal limits in all the tests performed. Moon⁴ has shown that in experimental hemorrhage the non-protein nitrogen is either unaltered or decreased. We, therefore, do not believe that bleeding alone can explain the marked urea nitrogen rise of Group B. The mild rise of urea N that occurred in Group A, and in the subject who ate beef protein after giving a transfusion can be explained as the ordinary increase expected following ingestion of a large amount of protein. On the other

hand, in Group B, the critical change in circulating fluid economy produced diminution in renal excretory function. This basic factor superimposed on the urea nitrogen increase due to large protein ingestion apparently causes the marked rise in urea nitrogen found in massive gastro-intestinal bleeding.

Summary. 1. A group of 5 normal adult males were each bled 580 cc. of blood and then drank the fluid. Periodic blood and urine examinations showed: (a) An average maximum increase in blood urea nitrogen of 24% above the fasting level, a slight decrease in plasma proteins and hematocrit index, a moderate increase in blood uric acid, phenols, and creatinine. (b) Normal urea clearance studies. (c) No systemic effects and black formed stools in nearly all cases.

2. A group of 3 adult normal males were each bled 800 cc. of blood and drank the fluid. Periodic blood and urine examinations revealed: (a) A marked elevation in blood urea N—90% above the fasting level, a moderate elevation of blood creatinine, phenols, and uric acid, a moderate fall in plasma proteins and hematocrit in-

dex. (b) A marked decrease in urea clearance compared to the experiments in A. (c) Moderate systemic effects for 24 hours.

Conclusion. Our results suggest a critical level at which blood lost from the vascular system and artificially "bled" into the intestinal tract produces no significant azotemia unless this level is exceeded. The level is somewhere between 580 and 800 cc. of whole blood. From this it appears that a gastro-intestinal hemorrhage greater than 580 cc. is necessary to produce the marked azotemia seen so frequently in bleeding peptic ulcers. Of course, the repeated loss at short intervals of a few hundred cc. of blood without compensatory regeneration, or else a slow, steady bleeding, would finally lead to a picture seen in acute massive hemorrhage into the bowel. The experimental work appears to support the contention of Black and of Johnson in that the azotemia of bleeding gastro-intestinal ulcers is primarily due to a fluid loss, sufficiently severe to impair normal renal function upon which is added the absorption of nitrogenous compounds from the enteral blood.

REFERENCES

1. BLACK, D. A. K.: Critical Review: Azotemia in Gastroduodenal Hemorrhage, *Quart. J. Med.*, 11, 77, 1942.
2. JOHNSON, J. B.: The Pathogenesis of Azotemias in Hemorrhage From the Upper Gastro-intestinal Tract, *J. Clin. Invest.*, 20, 161, 1941.
3. KAUMP, D. H., and PARSONS, J. C.: Extrarenal Azotemia in Gastro-intestinal Hemorrhage, *Am. J. Digest. Dis.*, 7, 191, 1940.
4. MOON, V. H., MORGAN, D. R., LIEBE, M. M., and MCGREW, D.: Similarities and Distinctions Between Shock and the Effects of Hemorrhages, *J. Am. Med. Assn.*, 117, 24, 2024, 1941.
5. SCHIFF, L., and STEVENS, R. J.: Elevation of Urea Nitrogen Content of Blood Following Hematemesis or Melena, *Arch. Int. Med.*, 64, 1239, 1939.
6. SCHIFF, L., STEVENS, R. J., GOODMAN, S., GARBER, E., and LUBBIN, A.: Observations on the Oral Administration of Citrated Blood in Man, *Am. J. Digest. Dis.*, 6, 597, 1939.
7. YUILE, C. L., and HAWKINS, W. B.: Azotemia Due to the Ingestion of Blood Proteins, *Am. J. Med. Sci.*, 201, 162, 1941.

A STUDY OF THE EFFECT OF BLEEDING AND OF REPEATED BLOOD DONATION ON SEROLOGIC TESTS FOR SYPHILIS*

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In December 1943 the Venereal Disease Subcommittee of the National Research Council recognized the impressions of several directors of Red Cross Donor Centers and other interested observers, to the effect that successive bleedings as such are capable of producing in some donors a non-specific positive reaction to recognized serologic tests for syphilis. To date we have seen no statistically valid data supporting this impression. Nevertheless the Subcommittee subsidized a special investigation. This was set up at the Institute for the Control of Syphilis, University of Pennsylvania, with the coöperation of the Philadelphia Red Cross Blood Donor Center. In its preliminary conferences, the group† charged with the work, broke down the project into two parts. In the first experiment, an unselected series of 98 seropositive donors was examined by all available means to determine the presence or absence of syphilis. This part of the study was essentially an examination of the positive serologic test with a view to its partitioning into specific and non-specific groups. From the non-specific group and from an examination of seropositive donors who had given more than one donation,

it was thought that a clearly defined group of multiple donor biologic false or non-specific positive reactors might be identified, whose reactivity might reasonably be ascribed to successive bleedings. The study failed to support the presupposition. It was impossible to prove and equally impossible to deny the existence of a multiple donation non-specific positive phenomenon.

The results of this study have been accepted as a report and prepared for publication under the title, "Non-specific Reactions in Routine Blood Testing for Syphilis; a Study of the So-called Biologic False Postive Reactions."

The proportion of positive serologic reactors in the whole material, and of presumptive *non-specific* positive reactors was so small that the question might well be raised as to whether the positives observed in multiple donors might not be simply laboratory technical false positives, and not the reflex of an actual biologic false positive phenomenon in a multiple donor.

Moreover the elimination of syphilis and the establishment of a convincing cause in an individual case for a bona fide non-specific positive proved to be undertakings

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania.

† In addition to the authors of this presentation, the following group participated in these studies: A. Parker Hitchens, M.D., Herman Beerman, M.D., Norman R. Ingraham, Jr., M.D., Louise E. Tavs, M.D., Virgene S. Wammock, M.D., Henry G. Morgan, Surgeon (R) USPHS, Stephen T. Whelan, M.D., Margaret J. Gerlach, M.D., on behalf of the Institute for the Control of Syphilis; Verner Nisbet, M.D., and Claude P. Brown, M.D., Director and Assistant Director respectively, Pennsylvania State Laboratory, Philadelphia; and the United States Public Health Service Venereal Disease Research Laboratory, John F. Mahoney, Medical Director, United States Public Health Service, Staten Island, New York.

of such extreme difficulty, that it was decided that no valid answer to the question could be had from the clinical-laboratory study short of years in time and millions in clinical case material.

It was therefore decided to set up Experiment 2 as a more controllable smaller-scale attack on the problem. A stable population source (prison inmates)* most of whom had given blood repeatedly, was bled under controlled conditions, and the serologic results collected. This material is the subject of the following report.

In order to conduct an investigation of the problem of the influence of bleeding on the serologic testing of blood, the American Red Cross Blood Donor Center arranged for a mobile unit trip to a nearby prison, thereby insuring a static group of donors which could easily be contacted again for follow-up. All donors at the institution had been previously screened by the prison physician in order to eliminate clinically those with recognizable syphilis.

One hundred sixty-four donors were accepted for bleeding, all of them men. Of these 27 were Negroes, the rest Whites. The ages varied from 18 through 58, preponderance of donors being between the ages of 21 and 40 years (Table 1).

TABLE 1.—AGES OF DONORS

Age	No.
18-20	1
21-25	40
26-30	40
31-35	25
36-40	31
41-45	15
46-50	7
51-55	2
56-60	3

Most of the donors had given blood before (see Table 2). For only 21 donors was this the first experience. Forty-three donors had donated blood more than 10 times.

The bleeding procedure used throughout was the prescribed procedure used in all Blood Donor Centers of the American

Red Cross. The area chosen for venepuncture was scrubbed with green soap followed by alcohol. A 2% aqueous solution of iodine was then applied and when it had been allowed to dry, was removed with alcohol. Procaine, 1%, was injected intracutaneously at the chosen site of venepuncture and after a few minutes actual venepuncture was made with a 15-gauge needle.

TABLE 2.—NUMBER OF DONATIONS GIVEN BY INDIVIDUALS

Times	No.
1	21
2	21
3	10
4	8
5	15
6	10
7	13
8	8
9	10
10	5
More than 10	43

As soon as bleeding was started, the lower end of the inlet tube was scrubbed with iodine and alcohol and a sterile 20-gauge needle inserted through this scrubbed area into the lumen of the tube. In this way, 10 cc. of whole blood was withdrawn into a syringe at the beginning of each venesection. The bleeding then continued in its normal fashion until the donor had given 500 cc. of blood at which time the bleeding bottle was clamped off, the tourniquet released and the needle removed from the vein. That amount of blood left in the inlet tube was then milked into a test tube to give us 8 to 10 cc. of whole blood. By following the above procedure we were able to collect samples of blood for study at the beginning and at the end of each venesection.

It is interesting to note here, that the procedure of inserting a sterile needle through cleansed rubber tubing in no way affected the sterility of the pint of blood withdrawn into the bleeding bottle. On checking with the processing laboratory, it was found that no contaminations had occurred in this shipment.

* We are indebted to Dr. Verne Burden, Medical Director and Chief Surgeon of the Eastern State Penitentiary, Philadelphia, and to the cooperating inmates, in this study.

All samples of blood taken at the end of venesection were sent to the processing laboratory where routine serologic testing was employed. This consisted of a Kahn and only those showing reaction were then followed up with a Kolmer. Serum that remained in sufficient quantity was then returned to us for study. We therefore had 128 samples that could be compared with those taken when venesection was begun. All reports from the processing laboratory were negative except one which was reported as Kahn plus 2, Kolmer plus 3.

On the 5th day following the donation of 500 cc. of blood, 10 cc. samples of blood were withdrawn from 38 of these donors (Group 1) chosen at random. Ten cc. samples were again withdrawn from the donors in this group on the 9th and 13th days.

Another group of 35 donors (Group 2) was seen on the 7th day after their donations of a pint of blood. From these too, we withdrew 10 cc. of whole blood and repeated this procedure on the 11th and 15th days.

Group 3 consisted of 24 donors tested once or twice from the 5th to the 15th day. The results obtained in Groups 1, 2 and 3 are shown in Table 1.

Serologic Procedures. Two tests were used in this experiment, one a *quantitative flocculation test* and the other a *quantitative complement fixation test*. The B.J.L. Macro flocculation test modified to detect at least $\frac{1}{4}$ of a unit was used. This technique is a modification of Lund's technique for determining small amounts of antibody (reagin), and is the same as that described by Boerner, Jones and Lukens except three dilutions of antigen were employed. Three tubes were used: the first carried 0.25 cc. of serum and 0.05 cc. of antigen emulsion; the second tube was the same except the antigen was diluted with an equal volume of saline before using; the third carried antigen that had been diluted to 4 times its volume with saline. Reactions in the first tube were given the value of 1 unit; in the second tube $\frac{1}{2}$ unit,

and in the third tube $\frac{1}{4}$ unit. Failure to obtain a reaction in any tube was recorded at no units which in this experiment means less than $\frac{1}{4}$ unit. We did not believe the detection of less than $\frac{1}{4}$ unit would be of any value in this study.

The quantitative complement-fixation technique employed was designed to determine the ability of serum to fix complement and differs from the usual methods in that the amount of complement was varied and the serum dose kept constant. We have called this technique the *fixation of complement test* to distinguish it from other quantitative complement fixation tests which titer the serum. The technique is similar to that used by Boerner and Lukens except three dilutions of complement (1:40, 1:60, 1:80) were substituted for the 1:30 dilution in the test itself. When fixation occurred in the 1:40 dilution, the test was repeated using eight dilutions of complement (1:10, 1:15, 1:20, 1:30, 1:40, 1:60, 1:80, and 1:120). For each dilution of complement a serum, antigen and hemolytic control was included.

The units of fixation are determined by reading and recording the amount of inhibition of hemolysis in each tube according to Table 3:

TABLE 3.—AMOUNT OF INHIBITION OF HEMOLYSIS

Amount, %			Unit of fixation
100	=	+4	1
75	=	+3	$\frac{3}{4}$
50	=	+2	$\frac{1}{2}$
25	=	+1	$\frac{1}{4}$
$12\frac{1}{2}$	=	=	$\frac{1}{8}$
Under $12\frac{1}{2}$	=	-0	0

Beginning with the strongest dilution of complement which shows at least $12\frac{1}{2}$ % inhibition of hemolysis in the serum control tube and no inhibition in the antigen control, calculate the specific fixation by subtracting the amount of inhibition in the serum control tube from the tube carrying antigen, using the values given above. To this figure add all the units of fixation in the tubes with stronger dilutions of complement.

Figuring from the 1:80 dilution, the

units in the serum and the antigen tubes would be $4\frac{1}{2}$ and the units in the controls $\frac{1}{8}$. The final reading would be $4\frac{1}{2}$ — $\frac{1}{8}$ or $4\frac{3}{8}$ units.

Experimental Material. A group of 164 donors was tested immediately before the withdrawal of blood, and 128 of these were tested at the end of bleeding to determine if the removal of 500 cc. of blood would cause any immediate change in the serologic tests.

Ninety-seven of the above group were tested at various intervals after donation to determine if any changes in the serologic tests occurred. In this study the donors are grouped into 3 groups as follows:

Group 1. Consisted of 38 donors tested on the 5th, 9th and 13th day following donation.

Group 2. Consisted of 35 donors tested on the 7th, 11th and 15th day following donation.

Group 3. Consisted of 24 donors tested once or twice from the 5th to the 15th day. The results obtained in Groups 1, 2 and 3 are shown in Table 1.

Results of the Fixation of Complement Test. In presenting the results of this study we have allowed $\frac{1}{2}$ a unit in the fixation of complement test for experimental error. Therefore, results reported as no units include all those having $\frac{1}{2}$ or less units, and the units given in other cases are the number in excess of $\frac{1}{2}$ unit.

The original test before bleeding (April 5, 1944) showed:

- 151 with $\frac{1}{2}$ or less units
- 6 with $\frac{1}{4}$ to 2 units
- 3 with $2\frac{1}{2}$ to $3\frac{1}{8}$ units
- 4 with 4 to $5\frac{1}{2}$ units

The 4 with high units failed to donate for the follow-up tests. It was later ascertained that at least 2 were old cases of syphilis. On May 15 we succeeded in obtaining blood from these 4 for re-testing. The following gives the results of the original test and the re-test on May 15:

No.	Original April 6 (units)	Re-test May 15 (units)
41103	5	$5\frac{1}{2}$
41104	5	$4\frac{1}{4}$
41107	4	$3\frac{1}{2}$
41075	$5\frac{1}{2}$	$2\frac{1}{2}$

The repeated test performed on 128 specimens collected immediately after bleeding showed 119 to give reactions identical with the original test before bleeding; 8 were within $\frac{1}{2}$ unit and 1 showed a difference of 1 unit.

The results obtained in Group 1 are shown in Table 5. Of the 38 donors tested, only 4 showed $\frac{1}{2}$ or more units in one or more of the tests. One (No. 41037) showed an increase in units having $\frac{1}{2}$ unit in the original test and $2\frac{1}{2}$ units 11 days later. This donor was subsequently tested on May 15, 1944, and showed $1\frac{1}{2}$ units.

The results obtained in Group 2 showed no increase in units from the 7th to 15th days after donation (Table 5). The 3 donors (Nos. 41073, 41113, and 41173) which showed 2 to 3 units were tested on May 15 (see Table 6).

The results in Group 3 are given in Table 5. All donors in this group gave $\frac{1}{2}$ or less units before and after donation of blood.

Results of the Flocculation Tests. In the original test before donation (April 6) of 164 donors all showed less than $\frac{1}{4}$ unit of flocculation with the exception of two (Nos. 41073 and 41077). A repeat test on 128 of these donors immediately after donation gave results identical with the original test before bleeding.

The re-tests of Groups 1, 2 and 3 were the same as the original and are shown in Table 3.

A number of these donors gave 2 to $5\frac{1}{4}$ fixation of complement units with less than $\frac{1}{2}$ unit of flocculation. Five of these failed to donate for the follow-up tests. On May 15 these donors were re-tested and the results are shown in Table 4. A record of at least 5 of these donors showed them to be old cases of syphilis.

The assumption that all these donors were non-syphilitic was based principally on the fact that they had given a number of donations with negative serologic reports. The results in Table 4 shows the inadequacy of using a single test as a screen. However, none of these cases was in the early stage of the disease and it is

unlikely that many early cases would be missed by screening.

On the other hand, it gives support to those who believe that at least 2 tests should be used as a diagnostic procedure and 1 of them a complement-fixation test.

Conclusions. 1. Blood donors (128) were tested by a quantitative flocculation and

complement-fixation test for syphilis, immediately before and immediately after bleeding. No significant difference in reagin content of the serum (antibody) was observed.

2. Blood donors (97) were tested for flocculation and complement-fixing reagin (antibodies) for syphilis before and at in-

TABLE 4.—EXAMPLES OF COMPLETED TEST

Complement	Serum antigen	Serum control	Antigen control	Hemolytic control
1:10	—	—	—	—
1:15	—	—	—	—
1:20	+2	—	—	—
1:30	+4	—	—	—
1:40	+4	—	—	—
1:60	+4	—	—	—
1:80	+4	±	—	—
1:120	+4	+3	+1	—

TABLE 5.—RESULTS OBTAINED IN 3 GROUPS

Group	Donor	After donation													
		Before donation		5 days		7 days		9 days		11 days		13 days		15 days	
		Floc (un.)	F-C (un.)	Floc (un.)	F-C (un.)	Floc (un.)	F-C (un.)	Floc (un.)	F-C (un.)	Floc (un.)	F-C (un.)	Floc (un.)	F-C (un.)	Floc (un.)	F-C (un.)
1	41115	0	1	0	0	0	1	0	1½		
	41138	0	½	0	0	0	1	0	½		
	41037	0	½	0	0	0	1½	0	2½		
	41163	0	0	0	0	0	0	0	½		
	34 donors	0	0	0	0	0	0	0	0		
2	41073	½	2	½	2	½	½	½	2
	41095	0	0	0	½	0	0	0	0
	41112	0	0	0	½	0	0	0	0
	41113	0	3	0	2½	0	2½	0	3
	41173	0	2½	0	2	0	2½	0	2
	41177	0	0	0	½	0	0	0	0
	29 donors	0	0	0	0	0	0	0	0
3	41109	0	0	0	½
	41049	0	0	0	½
	9 donors	0	0	0	0
	4 donors	0	0	0	0	0	0
	2 donors	0	0	0	0	0	0
	1 donor	0	0	0	0	0	0
	1 donor	0	0	0	0

TABLE 6.—ORIGINAL AND REPEATED TESTS ON SEROLOGIC POSITIVE DONORS

Case No.	No. donations*	April 6, 1944			May 15, 1944				Remarks
		Receiving station†	Floc (un.)‡	C-F (un.)‡	Floc (un.)‡	C-F (un.)‡	Kahn§	Kolmer§	
41103	15	Kahn-neg.	0	5	0	5½	Neg.	Pos. +4	
41104	11	Kahn +2 Kolmer +3	0	5	0	4½	Neg. ±	Pos. +4	Old treated syphilis
41107	2	Kahn-neg.	0	4	0	3½	Neg.	Pos. +3	
41075	7	Kahn-neg.	0	5½	0	2½	Neg.	Pos. +4	Old treated syphilis
41173	16	Kahn-neg.	0	2½	0	3½	Neg.	Neg.	Treated syphilis
41077	5	Kahn-neg.	0	2½	0	3½	Dbt. +	Pos. +4	Old treated syphilis
41113	5	Kahn-neg.	0	3	0	1½	Neg.	Neg.	
41073	13	Kahn-neg.	½	2	0	½	Neg. ±	Anticomp.	Old treated syphilis

* Previous donations to the Red Cross Blood Bank with negative Kahn tests.
† Tests performed at the processing laboratories.
‡ Tests performed at the Graduate Hospital, University of Pennsylvania.
§ Test performed at the United States Public Health Laboratory, Staten Island, New York.

tervals from the 5th to the 15th day following donation. One showed an increase of 2 fixation of complement units and none showed any increase in flocculation units.

3. Within the limits imposed by the conditions of the experiment, including the limited number of donors used, and by possible confusing elements such as intercurrent infections or other known causes of biologic false positives, and the fallibilities of the clinical examination for syphilis as performed, it can certainly not be said

that this series reveals the existence of a non-specific positive due to multiple blood donation, or to bleeding as such. Neither can it be said that such a possibility is totally excluded.

4. No statistically valid data are yet known to the investigators of this group which support the hypothesis that successive bleedings are capable of producing in some donors a non-specific positive reaction to recognized serologic tests for syphilis.

HEREDITARY HEMORRHAGIC TELANGIECTASIA

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HEREDITARY hemorrhagic telangiectasia is a definite clinical entity characterized by typical localized dilatation of small vessels to form angiomatous lesions, and a tendency to bleed from these areas. Telangiectases occur most commonly on the skin of the face and neck, and on the buccal and nasopharyngeal mucous membranes. It is an hereditary disease, being transmitted as a simple dominant. Both sexes are affected and both transmit the disease.

Babington¹ in 1865 described hereditary epistaxis. Rendu¹⁴ in 1896 reported a case of telangiectasia, and recognized the pathology and the hereditary aspect of the disease. At the turn of the century Sir William Osler^{11,12} did a great deal to establish telangiectasia as a clinical entity and to make it familiar to the profession. The literature on hereditary hemorrhagic telangiectasia was summarized by Goldstein⁷ in 1931, by Houser⁸ in 1934, and by Stock¹⁶ and by Barrock² in 1944.

The diagnostic criteria of hereditary hemorrhagic telangiectasia were established by Goldstein⁷ and affirmed by Larrabe and Littman.⁹ These are: definite hereditary tendency, visible typical telangiectases and a tendency to bleed from these lesions. A normal bleeding time, clotting time, clot retraction, platelet count and tourniquet test are usually considered essential for the diagnosis.

The lesion in this disease has been thought of as a local developmental defect of small vessels. Singer and Wolfson,¹⁵ in their study of a family with telangiectasia, suggested that a more fundamental capillary disturbance may be present. This hypothesis was based on the fact that their cases, in addition to typical telangiectasia, showed the unusual feature of a

positive tourniquet test. Singer and Wolfson¹⁵ classify them as pseudohemophilia, hereditary familial purpura simplex and hereditary hemorrhagic telangiectasia. Pseudohemophilia (von Willebrand¹⁷) is characterized by prolonged bleeding time, normal clotting time and clot retraction, a normal platelet count and a variable tourniquet test. Hereditary familial purpura simplex^{4,5} presents a positive tourniquet test, but a normal bleeding time. The characteristics of telangiectasia have been outlined.

In addition to the pure types of hereditary capillary bleeding syndromes described above, cases of one are seen with some of the features of another. The reported combinations of these diseases are depicted in Figure 1. This diagram is taken from Singer and Wolfson.¹⁵

Cases of pseudohemophilia are seen with a positive tourniquet test (indicating decreased capillary resistance) and also at times with deficient clot retraction; therefore, overlapping with hereditary familial purpura simplex. Singer and Wolfson's¹⁵ cases of hereditary hemorrhagic telangiectasia showed evidence of decreased capillary resistance (positive tourniquet test); hence, the overlap between hereditary familial purpura simplex and telangiectasia (Fig. 1).

As can be seen in Figure 1, there is no overlap between telangiectasia and pseudohemophilia, no case of telangiectasia with prolonged bleeding time having been reported previously. In their discussion of the capillary hereditary pathologies, Singer and Wolfson¹⁵ predicted the possibility of the occurrence of a prolonged bleeding time in hereditary hemorrhagic telangiectasia.

The purpose of this paper is to report 5 cases of hereditary hemorrhagic telangi-

ectasia all fulfilling the diagnostic criteria of Goldstein.⁷ In addition, they present various unusual associations. Two of these cases show prolongation of the bleeding time, thus fulfilling the prediction of Singer and Wolfson.¹⁵

The patient's parents were first cousins. Two maternal aunts had frequent epistaxes and menorrhagia. They were said to have died of hemorrhage from the nose. A maternal uncle had frequent epistaxes most of his life and died of hemorrhage from the

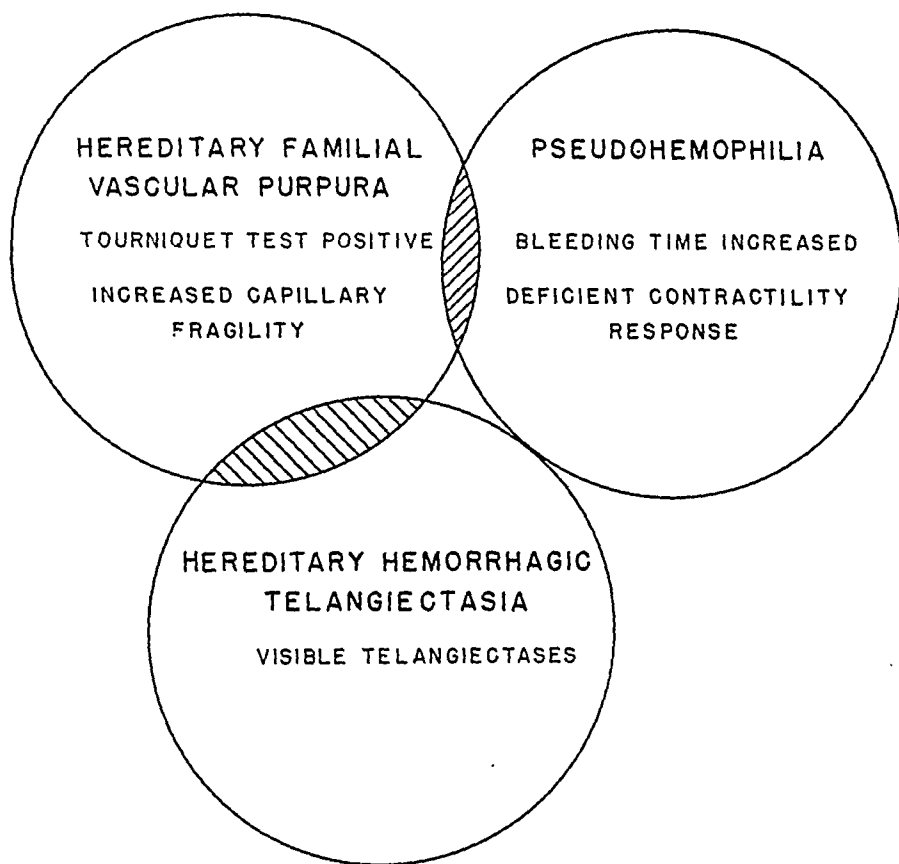


FIG. 1.—Diagram illustrating the various pure types and the reported combinations of hereditary capillary syndromes. The shaded areas represent the observed combinations. (Reproduced through the courtesy of the New England Journal of Medicine.)

Case Reports. CASE 1. A white, single female, aged 57, had frequent epistaxes and bleeding from the mouth as long as she could remember. Since the onset of her menses, there had been severe menorrhagia. Nine years before admission she had a profuse vaginal hemorrhage causing weakness and pallor. Roentgen ray sterilization was done with cessation of menorrhagia.

Three to 4 weeks before admission she began bleeding from the nose and mouth and vomited large amounts of blood. The day before admission uncontrollable hemorrhage from the nose occurred. She became weak and pale, and was admitted to the hospital in a state of shock.

nose. One brother, aged 65, had numerous nosebleeds throughout most of his life until 10 years ago.

Physical examination on admission revealed the signs of shock due to blood loss, for which she was successfully treated. The skin was pale, and showed several purpuric areas over both lower extremities. On superficial examination no telangiectases were seen. The liver and spleen were not palpable. Otolaryngologic consultation revealed fairly large dilated thin-walled veins in the region of the posterior nares. These were more marked on the left side, and the left turbinate was very hyperemic.

Laboratory studies on admission showed a red blood cell count of 1,340,000 per c.mm., a white blood cell count of 18,850 per c.mm., and a hemoglobin of 5 gm. %. Following a series of transfusions the red blood cell count was 4,890,000 per mm. and the hemoglobin 12.4 gm. %. The blood smear was normal with an abundance of platelets. The bleeding time on 2 occasions was 6 minutes and $6\frac{1}{2}$ minutes, respectively. The coagulation time on 4 determinations was normal, ranging from 1 to 5 minutes. Clot retraction on 2 occasions was satisfactory in from 2 to 3 hours. One week later clot retraction was poor after 24 hours. The tourniquet test on 2 occasions showed 16 and 18 petechiæ respectively per 2.5 cm. area. The prothrombin time was normal (method of Quick) and the plasma fibrinogen was 0.36 gm. %.

This case presented all the criteria for the diagnosis of hereditary hemorrhagic telangiectasia, *i. e.*, an hereditary tendency, visible telangiectases, and bleeding from these lesions. In addition, a prolonged bleeding time, and a positive tourniquet test were present. Clot retraction was variable.

CASE 2. A white female, aged 40, had no hemorrhagic tendency prior to 9 years before admission when she had severe bleeding from the nose lasting several days. This was associated with weakness and pallor. At intervals from that time until admission she had profuse epistaxes and several times had spontaneous hemorrhage from the mouth. Six years before admission she experienced a severe postpartum hemorrhage, but had no excessive bleeding following several other deliveries. For $1\frac{1}{2}$ years prior to admission she had irregular menstrual periods associated with menorrhagia. Very frequent vaginal bleeding was present for 3 months prior to admission. She entered the hospital bordering on shock from blood loss due to hemorrhage from the uterus.

The patient's father and 1 paternal aunt had frequent profuse epistaxes throughout most of their lives. Three of 4 of the patient's children have excessive hemoptyses.

Physical examination on admission revealed her to be very pale with cold, moist skin and a rapid, thready pulse. The blood pressure was normal. Scattered over the skin of the face, neck, arms and thorax were numer-

ous telangiectases. Definite dilated vessels were seen in the mucosa of the nasal septum, and several small telangiectases were present on the hard palate. The liver was felt 3 cm. below the costal margin in the right mid-clavicular line. The spleen was easily felt 3 cm. below the costal margin.

Laboratory studies on admission revealed the red blood cell count to be 1,300,000 per c.mm. and the hemoglobin was 2.7 gm. %. The white blood cell count was 7500 per c.mm. The blood smear showed a scarcity of platelets. A platelet count was 46,800 per c.mm. The anemia was corrected with transfusions of whole blood. Four blood smears while the patient was in the hospital showed a paucity of platelets. Seven platelet counts ranged from 3000 to 46,800. Other blood studies are shown in Table 1.

The tourniquet test was completely negative on 1 occasion and 15 months later showed 12 petechiæ per 2.5 cm. area, the same degree of hemostasis being used both times. Clot retraction was satisfactory on 1 occasion, and poor on 2 others. The clotting time was normal while under observation in the hospital, and definitely prolonged 15 months later.

After discharge from the hospital she had no more epistaxes and only slight menorrhagia. Fifteen months after discharge her red blood cell count and hemoglobin were normal. Other blood studies are shown in Table 1.

This case demonstrated hereditary hemorrhagic telangiectasia with a consistently prolonged bleeding time. In addition there was definite thrombocytopenia.

CASE 3. A white female, aged 49, gave a history of frequent epistaxes and hemoptyses for many years. The patient's grandmother, mother, 1 maternal aunt, 2 siblings, and her 2 children all had frequent epistaxes. Several of the above relatives were examined and found to have typical telangiectases over the skin of the face, neck and on the nasal mucous membrane.

At age 18 the patient had migrating polyarthritides associated with fever and weakness.

On *physical examination*, scattered linear, spider-like and nodular telangiectases were seen over the thorax, arms, neck and face. In the skin over the right arm were several small purpuric spots. Dilated vessels were

seen in the nasal mucosa. A few medium moist râles were heard at the left lung base. The heart was markedly enlarged, with physical signs of mitral stenosis and insufficiency. The liver and spleen were not felt.

Laboratory findings included a red blood cell count of 4,400,000 per c.mm., a white blood cell count of 6200 per c.mm., and a hemoglobin of 13.2 gm. %. The blood smear appeared normal with adequate numbers of platelets. Platelet counts were normal. The bleeding time was 3 minutes and the clotting time was 5½ minutes. The tourniquet test showed innumerable petechiæ after 10 minutes with the cuff inflated to a pressure midway between the systolic and diastolic blood pressures. Repeated sputum examinations showed no acid-fast organisms. Roentgenographic examination of the chest including bronchograms revealed no pulmonary lesion.

A family history was obtained of frequent epistaxes in the patient's son, 2 brothers, 1 sister and several nephews.

On *physical examination*, numerous telangiectases were found on the face. Dilated vessels were seen on the right side of the nasal septum and a plexus of dilated vessels was present at the posterior tip of the left inferior turbinate. The liver and spleen were palpable.

Laboratory studies included a red blood cell count of 5,200,000 per c.mm. and a white blood cell count of 6550 per c.mm.; hemoglobin was 12 gm. %. The blood smear was normal with an abundance of platelets. The bleeding time was 2.5 minutes and the clotting time was 2 minutes. Clot retractility was normal. The tourniquet test was negative and the platelet count was 721,000 per c.mm.

Examination of the patient's son revealed

TABLE 1.—STUDIES ON CASE 2 IN HOSPITAL AND 15 MONTHS FOLLOWING DISCHARGE

Date	Bleeding time (min.)	Clotting time (min.)	Clot retraction	Tourniquet test
Jan. 4 . . .	4.5	4.0	Satisfactory	
Jan. 14 . . .	7.0	7-8	None at 12 hr.; slight at 24 hr. (room temp.)	No petechiæ after 30 min. at 50 mm. Hg pressure
Jan. 19 . . .	6.5	2.5		
April 2 . . . 1 year later	11.0	14.0	Poor	12 petechiæ in 20 min. at 50 mm. Hg pressure
April 30 . . . 1 year later	5.0	16.0		

The patient has been seen in the clinic at intervals for the past 7 years since discharge from the hospital. There has been a decrease in the hemorrhagic tendency, and she is being treated for mild chronic congestive heart failure.

This case presented a classical picture of hereditary hemorrhagic telangiectasia. In addition, increased capillary fragility, shown by a positive tourniquet test, was present. Associated was rheumatic heart disease.

CASE 4. A white female, aged 46, was admitted to the hospital with a history of repeated nosebleeds since the age of 10. Nine years before admission a hemorrhage from the nose occurred necessitating transfusion. Since the onset of menses she had had severe menorrhagia.

well-marked telangiectases on the face and left side of the nasal septum.

This is a typical case of hereditary hemorrhagic telangiectasia.

CASE 5. An electrician, aged 33, was admitted to the hospital because of bleeding from the throat. He gave a history of frequent epistaxes beginning at the age of 15. Lesions on the lower lip that would bleed at frequent intervals were noted by the patient as long as he could remember. Eight days before admission he began to bleed from the mouth and cough up large clots of blood. This persisted until admission.

He gave a family history of frequent hemorrhages from the mouth and nose in his daughter, his father, 1 brother and 1 sister.

On *physical examination* there were striking telangiectases on the lower lip and on

the posterior pharyngeal wall. Excoriated areas were seen on both sides of the nasal septum. The remainder of the physical examination was essentially negative.

Laboratory findings showed a red blood cell count of 4,850,000 per c.mm., a white blood cell count of 9000 per c.mm. and a hemoglobin of 11.2 gm. %. The blood smear was normal with adequate numbers of platelets. The bleeding time was 1 minute and the clotting time was $2\frac{1}{2}$ minutes. Clot retrac-

tion time. The coagulation time in 1 case was prolonged on 2 occasions, and normal on several others. Clot retraction was variable in 2 patients. The tourniquet test was positive in 2 cases, equivocal in 1, variable in 1, and negative in 1. Platelets were described as numerous in 2 of these patients, normal in 2, and definitely decreased in 1 case.

A normal bleeding time, clotting time,

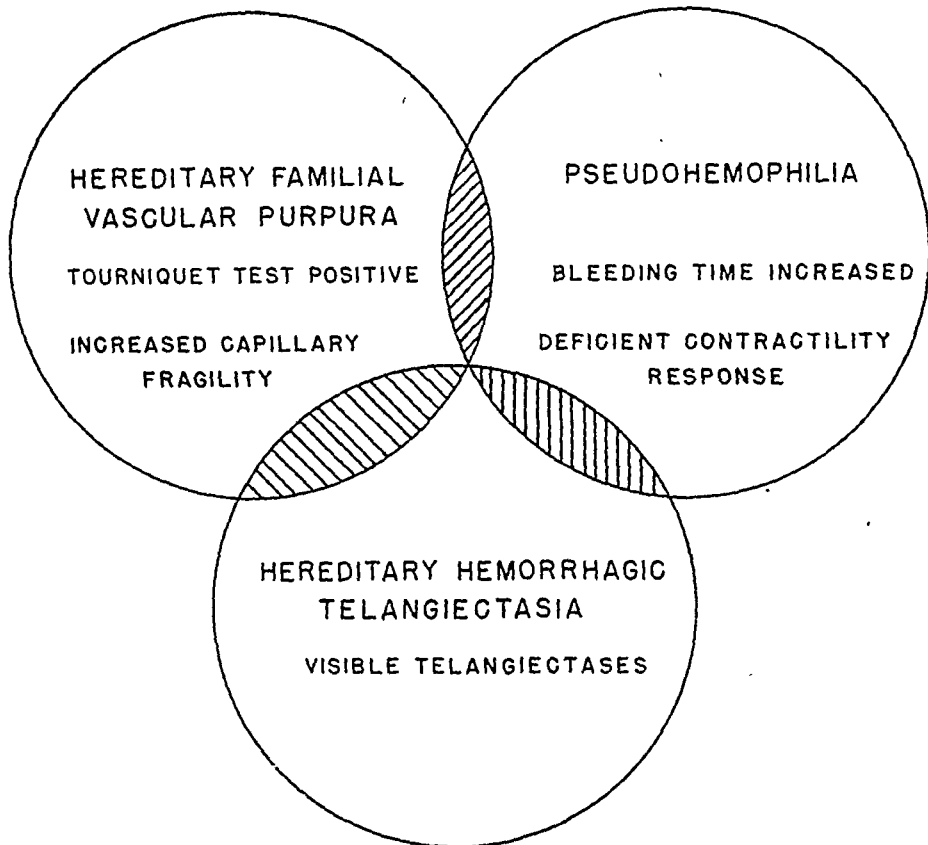


FIG. 2.—Modification of Figure 1 illustrating more complete interrelationship between the hereditary capillary syndromes.

tion was slight at 24 hours. The tourniquet test revealed an average of 10 petechiae in a 2.5 cm. circle after 15 minutes with the blood pressure cuff midway between the systolic and diastolic pressures.

This case presented classical hereditary hemorrhagic telangiectasia associated with poor clot retraction and a borderline tourniquet test.

Comment. Five cases are presented, all satisfying the diagnostic criteria of hereditary hemorrhagic telangiectasia. In addition, 2 of these showed prolongation of the

clot retraction, platelet count, and the tourniquet test are usually found present in hereditary hemorrhagic telangiectasia. Classification of bleeding syndromes in tables of differential diagnosis^{13,18} are based largely on the above tests. That no such rigid form of classification is applicable has been pointed out.^{6,15}

Cases 1 and 2 present all the criteria for the diagnosis of hereditary hemorrhagic telangiectasia. In addition, the bleeding time was prolonged in both cases. Singer and Wolfson¹⁵ presented an analysis of the

pathologic physiology of the capillary bleeding syndromes. They regarded an abnormal response of a capillary to injury¹⁰ (expressed by a prolonged bleeding time), and increased capillary fragility (expressed by a positive tourniquet test) as unrelated abnormalities that may occur independently or together. These two abnormalities exist independently in the pure types of pseudohemophilia and hereditary purpura simplex. The abnormalities exist together in the reported combinations (see Fig. 1). Singer and Wolfson¹⁵ found cases of telangiectasia with a positive tourniquet test (increased capillary fragility) and reasoned by analogy that telangiectasia with a prolonged bleeding time (defective capillary retractility)¹⁰ could occur. Cases 1 and 2 fulfill their prediction. The interrelationship shown in Figure 1 may now be completed as shown in Figure 2.

It is seen that definite thrombocytopenia is present in Case 2. In the presence of thrombocytopenia, to attribute prolonged bleeding time to deficient capillary contractility may invite criticism. However, the exact mechanism of the platelets in hemostasis is not known and there is not always a correlation between thrombocytopenia and increased bleeding time.^{3,10} The tourniquet test in this case was negative in association with thrombocytopenia and a prolonged bleeding time. This is evidence of deficient capillary contractility.¹⁰

Cases 1 and 2 showed a definitely positive tourniquet test. In Cases 2 and 5

the tourniquet test was borderline. Singer and Wolfson¹⁵ pointed out the association of increased capillary fragility in association with typical telangiectasia, reporting 3 cases. They could find only 1 family in the literature of hereditary hemorrhagic telangiectasia associated with a positive tourniquet test. This family had hereditary familial purpura simplex associated with telangiectasia and was reported by Davis.⁴

In Cases 1 and 2 there was variability in some of the tests from one time to another. The clot retractility in both cases was satisfactory on some occasions and deficient on others. In Case 2 the clotting time varied, being normal while the patient was in the hospital and definitely prolonged 15 months later. The tourniquet test in Case 2 was negative on 1 occasion and borderline on another (Table 1). These variations in the hereditary bleeding syndromes have been observed and emphasized.⁶

Summary. 1. Five cases of hereditary hemorrhagic telangiectasia are presented.

2. Deficient capillary contractility and decreased capillary resistance are observed in association with telangiectasia.

3. Variations in other tests of the hemostatic mechanism usually considered normal in telangiectasia are observed in this disease.

4. That hereditary hemorrhagic telangiectasia is a fundamental capillary disturbance is supported.

REFERENCES

1. BABINGTON, B. G.: *Lancet*, **2**, 362, 1865.
2. BARROCK, J. J.: *Wisconsin Med. J.*, **43**, 805, 1944.
3. BEDSON, S. P.: *J. Path. and Bact.*, **25**, 94, 1922.
4. DAVIS, E.: *Lancet*, **2**, 1110, 1939.
5. DAVIS, E.: *Lancet*, **1**, 145, 1941.
6. GEIGER, A. J., and EVANS, A. G.: *Internat. Clin.*, **2**, 135, 1938.
7. GOLDSTEIN, H. I.: *Arch. Int. Med.*, **48**, 836, 1931.
8. HOUSER, K. M.: *Ann. Otol., Rhinol. and Laryngol.*, **43**, 731, 1934.
9. LARRABEE, R. G., and LITTMAN, D.: *New England J. Med.*, **207**, 1177, 1932.
10. MCFARLANE, R. G.: *Quart. J. Med.*, **10**, n.s., **1**, 1941.
11. OSLER, W.: *Bull. Johns Hopkins Hosp.*, **12**, 333, 1901.
12. OSLER, W.: *Bull. Johns Hopkins Hosp.*, **18**, 401, 1907.
13. QUICK, A. J.: *The Hemorrhagic Diseases and the Physiology of Hemostasis*, Springfield, Ill., Charles C Thomas, 1942.
14. RENDU, M.: *Bull. et mém. Soc. med. hôp. de Paris*, **13**, 731, 1896.
15. SINGER, K., and WOLFSON, W. Q.: *New England J. Med.*, **230**, 637, 1944.
16. STOCK, M. F.: *Arch. Otolaryngol.*, **40**, 108, 1944.
17. VON WILLEBRAND, E. A.: *Finska Lakaresallsk. Handl.*, **68**, 87, 1926.
18. WINTROBE, M. M.: *Clinical Hematology*, Philadelphia, Lea & Febiger, 1942.

BRONCHOPULMONARY GEOTRICHOSIS

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ACCORDING to Dodge,⁴ *geotrichum* is a sub-species of *eremnascaceae Imperfectae*, and was first described by Link in 1809. In many respects it resembles *blastomyces dermatitidis* and *coccidioides immitis*. It has frequently been confused with the more pathogenic *blastomyces dermatitidis*.⁹ The genus is quite large, the species being mostly saprophytic on earth and decaying organic matter. According to Dodge,⁴ until 1935 12 cases had been reported in man, 8 from infections of the respiratory tract, 3 from stools, parasitism unknown, and 2 from blastomycosis.

In 1933 Smith⁹ reported 5 non-fatal infections due to *geotrichum* and gave the essential cultural characteristics necessary for identification of the fungus. He emphasized that patients with clinical symptoms of chronic bronchitis or pulmonary tuberculosis, who have white mucoid sputum containing grayish flakes, should be suspected of having an infection with the yeast-like or mold-like fungus *geotrichum*. The organisms can be cultured from the sputum on Saboraud's media, and identified by the rectangular conidia.

deAlmeida and DaSilva³ recently isolated 4 strains of *geotrichum* from the sputum of patients presenting pulmonary symptoms, and they discussed the frequency of false yeast isolated from sputum of patients with similar symptoms.

Of 79 cases of bronchopulmonary mycosis reported by Reeves⁸ recently only 1 was a case of *geotrichum* infection. Recent excellent articles by Gill,⁵ Johnston and Heydemann⁶ and Peterson⁷ on pathogenic molds and the lesions they produce

in the respiratory tract, failed to mention infection by *geotrichum*.

We are reporting our case not only because bronchopulmonary *geotrichosis* is of rare occurrence, but because we believe that any light that can be thrown on the recognition of any of the fungus diseases will curtail erroneous diagnoses of pulmonary tuberculosis and non-specific pulmonary disease.

Case Report. This 22 year old colored soldier was admitted to Ashford General Hospital on July 16, 1944 with the following history: he entered the Army on Dec. 2, 1942 and felt well until the early part of Feb., 1944 when he complained of sharp pains in his left lower chest which disappeared in a few days.

This soldier had been with a cavalry regiment stationed in Western Texas in Jan. 1944, approximately 1 month before the onset of his present illness. There is no history of previous pulmonary disease or known contact with tuberculosis.

In April, 1944, shortly after arriving in North Africa, he had a recurrence of pain in his left chest lasting for 3 days accompanied by night sweats, weakness and a cough productive of small amounts of mucoid sputum. There was no hemoptysis. He lost 10 to 15 pounds in about 6 weeks.

On April 18, 1944, he was admitted to a station hospital in North Africa. Here a friction rub was heard over the left chest in the axillary line. His sedimentation rate was normal; sputum examination revealed no tubercle bacilli or fungi. The plasma proteins were normal. The blood count was normal and the urine revealed no abnormal findings. A Roentgen ray of the chest showed "a diffuse mottling throughout both lung fields that had the appearance of pulmonary

infiltration. The etiology may be fungus or tbc. in nature." (Fig. 1). During the 17 days spent in this hospital he complained of moderate pain in his left chest. His sputum was scanty, he ran a maximum temperature up to 99° the first 2 days only, and his general condition remained "excellent." On May 25, 1944, he was transferred to a general hospital with a diagnosis of probable coccidioidomycosis contracted in Texas.

suggests metastatic tumor in spite of the fact that the lesions are not sharply outlined or uniform in shape. A radiograph of the skull shows no cranial or intracranial abnormalities." A final Roentgen ray of the chest taken on June 9, 1944, showed "slight clearing of the patchy inflammatory process in both lungs since May 22. No cavities can be identified." (Fig. 2.)

On July 7, 1944, he was evacuated to the

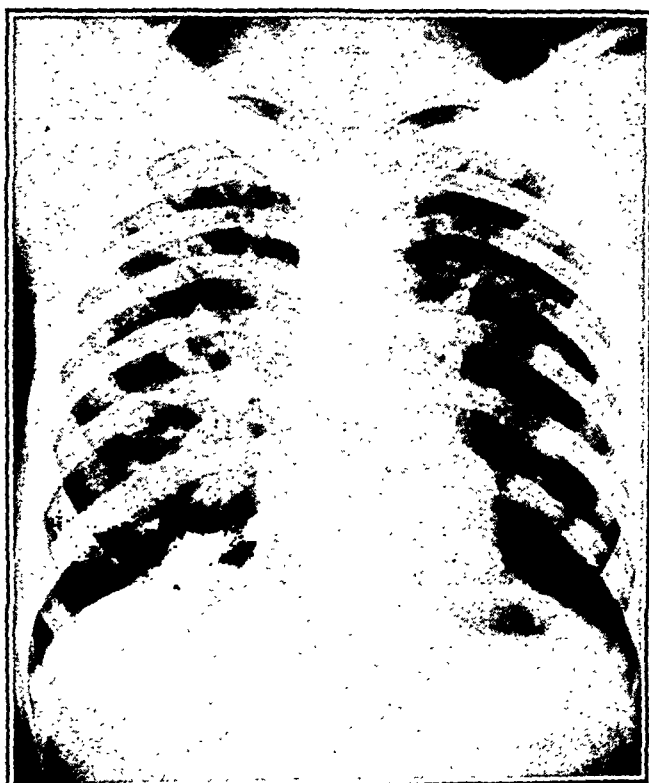


FIG. 1.—Roentgen ray of the chest, April 18, 1944, shows a diffuse mottling throughout both lung fields giving the appearance of "soft infiltrations." There is moderate enlargement of the hilar lymph nodes bilaterally.

Further studies were done to exclude a primary neoplasm with metastasis to the lungs. A complete G.I. series and intravenous pyelogram revealed no abnormalities. The sedimentation rates were normal, the blood counts and urinalyses were normal and repeated examination of the sputum revealed no tubercle bacilli or fungi. The radiologist reported that "Chest radiographs made elsewhere on April 19, and on May 7 and 22, show an extensive disseminated bilateral patchy pulmonary infiltrative process which seems to be progressive; the appearance is not characteristic, but rather

United States for further observation and treatment.

Physical examination on July 17, 1944, revealed a well developed and well nourished colored male who weighed 161½ pounds (160 normal). He did not appear ill. The thorax was well developed and symmetrical and expansion was good. Harsh, rasping breath sounds were heard over the entire chest posteriorly. No friction rub was heard. The heart was normal, the blood pressure was 124/72. The skin was clear, the skeletal system appeared normal and

there was no adenopathy. The liver and spleen were not enlarged.

Laboratory Findings. Roentgen ray film of the chest shows infiltrations throughout both lung fields with little change as compared with the film of June 6, 1944 (Fig. 3).

Blood:

RBC	4,540,000
Hb	16.5 gm.
WBC	4700
Neut.	50
Lymph.	40
Mono.	9
Eos.	1
NPN	30.0 mg. per 100 ml.
Total protein	6.6 gm. per 100 ml.
Albumin	4.6 gm. per 100 ml.
Globulin	2.0 gm. per 100 ml.
A/G ratio	2.3

Sputum—Repeated 24-hour concentrates negative for tubercle bacilli; 3 successive gastric washings negative for tubercle bacilli; 3 sputum examinations and 3 gastric washings on July 27 and 31 and Aug. 1, revealed a species of fungus Imperfecta, *Geotrichum*.

Progress. This patient was given 15 gr. of sodium iodide intravenously daily and 20 drops of saturated solution of potassium iodide orally 3 times a day for the first week. The sodium iodide was then increased to 30 gr. and the saturated solution of potassium iodide increased to 120 drops a day. A total of 35 gm. of sodium iodide intravenously was given, following which he con-

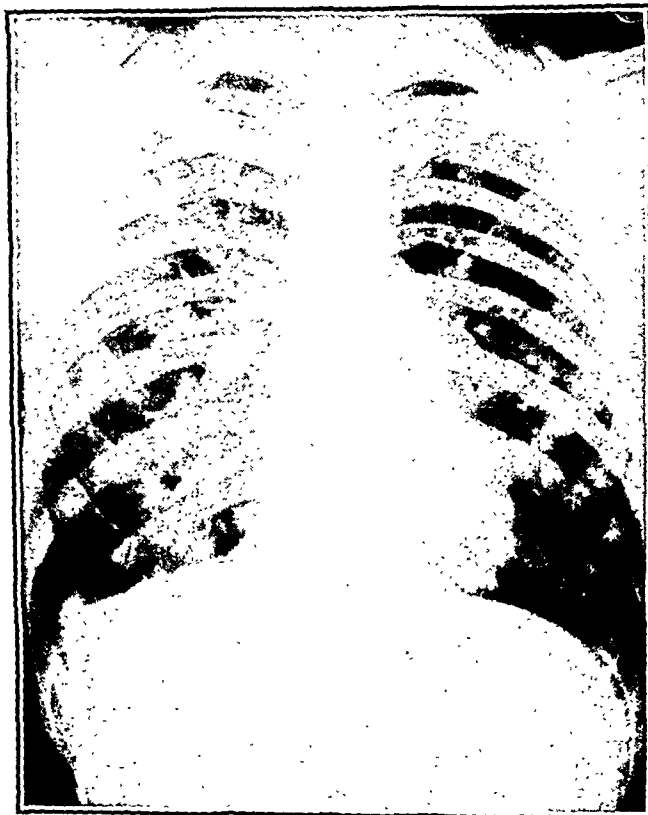


Fig. 2.—Roentgen ray of the chest June 6, 1944, shows slight clearing of the infiltration noted on April 18, 1944.

Sedimentation Rate—2mm/30 min. Westergren.

Urinalysis—negative.

Coccidioidin Intradermal Test—Negative in dil. 1-1000, 1-100, 1-10.

Tuberculin Test—Negative in dil. 1-100,000, 1-10,000.

tinued on saturated solution of potassium iodide until there was complete clearing of the pulmonary lesions. During treatment he showed a remarkable improvement radiologically and in a period of 3 months there was complete clearing of the pulmonary infiltrations (Fig. 4). Improvement was



FIG. 3.—Roentgen ray of the chest, July 17, 1944, shows little change in the appearance of the lungs as compared with film of June 6, 1944.

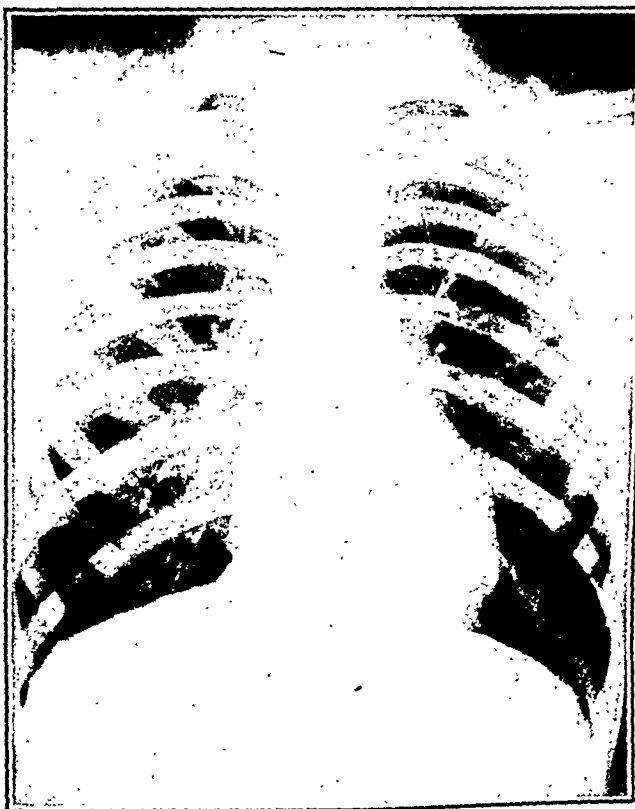


FIG. 4.—Roentgen ray of the chest, Nov. 11, 1944, shows complete clearing of the pulmonary infiltrations, decrease in size of the hilar lymph nodes, and slight increase in the bronchial markings extending out from the right hilar region.

noticed after 1 week of therapy and the sputum became negative for fungi during the first week of treatment. He regained the 10 pounds he lost, his cough disappeared, and his general condition became excellent. At the time of this writing, he is taking part in Group III reconditioning program and will be sent back to duty of a limited nature.

Discussion. The increased frequency with which mycotic disease of the lungs is being reported in the literature probably indicates a sharpening of diagnostic acumen rather than an actual rise in the incidents of mycotic disease in general. Frequently mycotic disease is being salvaged from the waste basket of non-specific pulmonary disease, atypical pneumonitis, and unproved pulmonary tuberculosis.

there seems to be sufficient similarity in lesions produced to warrant discussion of the histological tissue findings, Roentgen findings, and sequelæ of all yeast infections as though they were a single entity and any variation one only of degree of variance and not necessarily characteristic for the species. However, we believe that identification of the species is of importance in selecting therapeutic measures.

From the standpoint of symptomatology and clinical findings there is nothing significant in regard to geotrichum infection to differentiate it from other types of mycotic disease. Peterson⁷ recently justifiably stated that "any lesion having the appearance of tuberculosis in which no tubercle bacilli can be found, should be studied carefully to rule out a fungus in-

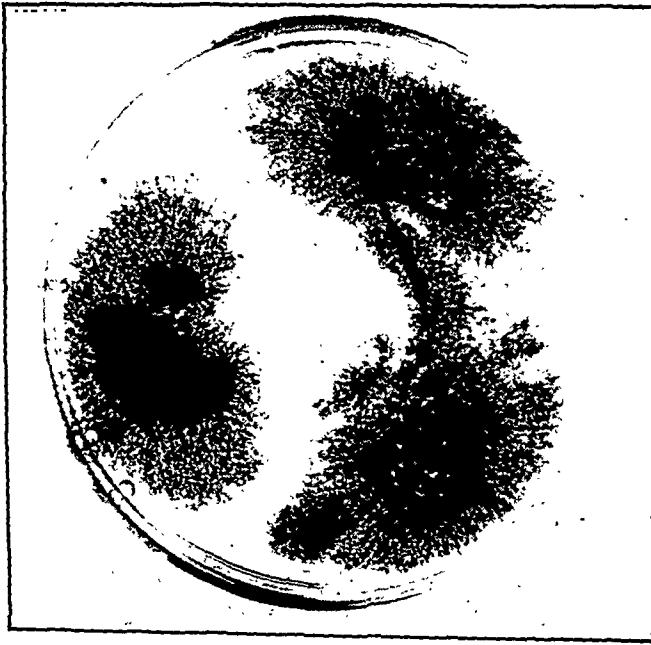


FIG. 5.—Four day old colonies from sputum on Sabouraud's agar at room temperature.

It is true that yeast organisms may "contaminate" the respiratory tract as non-pathogenic organisms, and also sputum specimens in the laboratory. However, it is also recognized that they may act as both primary and secondary pathogenic invaders, more often the latter.

Campbell,² following a study of a good number of yeast infections of the lung, believes that from a practical standpoint

infection. In patients in whom no definite organisms can be isolated, a therapeutic test with iodine may be instituted and the final diagnosis based on the response." A white mucoid sputum containing grayish flakes, having an yeast-like odor should suggest a fungus disease.⁹ Further identification of the type will have to be made on the basis of cultural characteristics.

Macroscopically the organism is grown

on Sabouraud's media—the colony is developed in 24 to 48 hours at room temperature. They are small, white, fuzzy and adherent to the agar (Fig. 5). Giant colonies develop in 10 days and show a radiating appearance with abundant *cor-emia* (Fig. 6). The strain isolated repeatedly from the sputum of our patient liquefied both gelatin and litmus milk. Acid was formed from dextrose, maltose, sucrose and lactose. This strain of *geotrichum* shows some of the characteristics of *G. Versiforme* (Dodge⁴).*

persed as to resemble bacterial forms characteristic of *geotrichum*.

It is highly important that repeated examination of the sputum for tubercle bacilli be performed before tuberculosis is eliminated. Not infrequently tuberculosis may coexist with fungus disease. In our case, both the tuberculin and the coccidioidin skin tests were negative.

Recently *geotrichum* was isolated from the sputum of 2 other cases of chronic respiratory tract disease. In 1 case bronchiectasis and asthma were suspected;

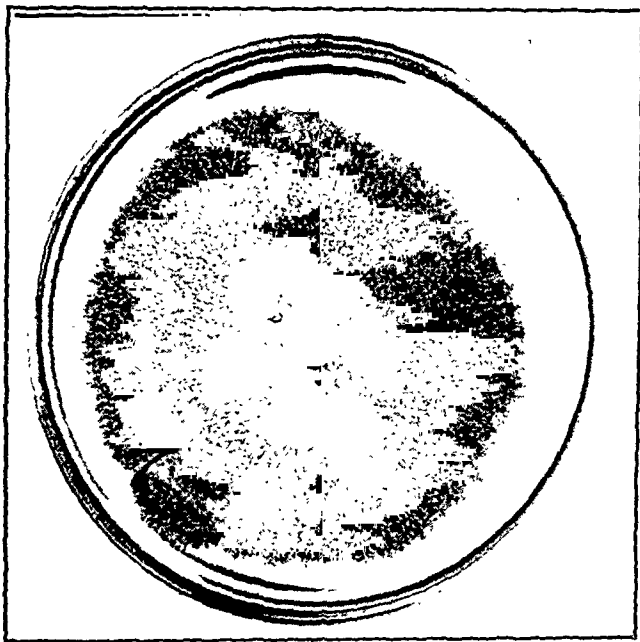


FIG. 6.—Ten day old giant colony on Sabouraud's agar at room temperature.

Microscopically the mycelium is septate and displays both arthrospores and chlamydospores. The arthrospores are very abundant in young (2 days) preparations and appear as bacillary and coccoidal forms at 440 diameter magnification. Baker, *et al*¹ in 1943 considered *geotrichum* as a variety of *coccidioides*. However, culture of several *coccidioides immitis* studied here and those described by Dodge⁴ did not show the conidia or arthrospores so dis-

both were ruled out on the basis of normal lipidol studies and inconclusive skin tests for protein sensitivity. However, a chronic bronchitis was present which, from the history, evidently followed an atypical pulmonary infiltration which he developed while in North Africa. It is interesting that recent skin tests revealed that he was sensitive to several molds including *aspergillus*, *monilia*, and *penicillium*. The second case also was one of chronic

* The Army Medical School and The Fungus Laboratories of Duke University confirmed the diagnosis of *geotrichum*. A recent communication from Norman F. Conant, Ph.D. of the Department of Medicine, Duke University, stated that the fungus was identified as *geotrichum sp.*, a generic identification only, since the exact species could not be identified.

bronchitis with asthmatic symptoms who showed nothing definite on skin testing, but who repeatedly showed geotrichum in his sputum. Radiologic examination of both patients showed no evidence of pulmonary parenchymal involvement.

Conclusion and Summary. Geotrichum has been isolated repeatedly from the sputum of 3 patients, 1 of whom presented symptoms and radiologic findings of chronic bronchopulmonary disease; the other 2 presented symptoms of chronic bronchitis and asthma with no evidence of pulmonary infiltration. The clinical findings and the radiologic appearance of the lesions are not specific for geotrichum alone, but are not unlike those of mycotic disease in general. Furthermore, the symptoms and clinical findings may readily be confused with tuberculosis and atypical pneumonitis. An accurate diagnosis is

important from the standpoint of treatment and disposition of the patient. Geotrichum apparently responds well to massive iodide therapy with complete clearing of the lesions and disappearance of the bronchopulmonary symptoms.

It is realized the spontaneous resolution of mycotic pulmonary lesions not infrequently occurs in mild infections. Spontaneous improvement occurred in the case herein reported. However, we have every reason to believe that clinical recovery and disappearance of the fungus from the sputum was expedited by the iodide therapy. It is true that secondary infection coexists with or complicates fungus disease altering the clinical picture and retarding the recovery of the patient. Fortunately, our patient has no apparent secondary infection to interfere with recovery.

REFERENCES

1. BAKER, É. E., MEAK, E. M., and SMITH, C. E.: The Morphology, Taxonomy and Distribution of *Coccidioides Immitis*, Rixford & Gilchrist, 1896, Farlowia, 1 (2), 199, 1943.
2. CAMPBELL, SETON: Actinomycosis of the Lungs, Royal Society of Medical Proceedings, 30, Part II, 876, 1936.
3. DEALMEIDA, F., and DASILVA, LACAZ, C.: Mycologic Study of Four Strains of Geotrichum Isolated From Sputum, Folia. Clin. et Biol., 12, 41, 1940.
4. DODGE, WILLIAM CARROLL: Medical Mycology: Fungus Diseases of Men and Other Mammals, Washington University, St. Louis, C. V. Mosby Company, p. 217, 1935.
5. GILL, WM. D.: Pathogenic Molds and the Lesions They Produce in the Respiratory Tract, Trans. Am. Laryngol. Assn., 63, 217, 1941.
6. JOHNSTON, WAYNE A., and HEYDEMANN, JULIUS: Clinical and Radiologic Studies of Pulmonary Mycosis, Radiology, 43, 1, 1944.
7. PETERSON, VERNON L.: Fungus Diseases of the Chest, Radiolog, 43, 14, 1941.
8. REEVES, ROBERT J.: The Incidence of Bronchomycosis in the South, Am. J. Roentgenol. and Rad. Ther., 45, 513, 1941.
9. SMITH, DAVID T.: Oidiomycosis of the Lungs, J. of Thorac. Surg., 3, 241, 1934.

THE PENETRATION OF ANTIBACTERIAL SUBSTANCES INTO ISCHEMIC, INFLAMMATORY TISSUE

WITH A CONSIDERATION OF THEIR USE IN SHOCK OF BACTERIAL ORIGIN*†

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THE incidence of war wounds involving trauma to muscles stimulated renewed interest in the mechanism of the shock syndrome which often follows such injury. In an endeavor to ascertain the causes of shock due to muscle injury alone, a method was devised in this laboratory¹⁵ which made it possible to produce shock regularly in dogs (50 out of 52 animals) by crushing a known amount of muscle. Bleeding was minimal. In this procedure, the quadriceps femoris of anesthetized animals was removed from one hind limb under sterile precautions, ground in a sterile mortar and replaced in its original bed. After operation, the limb became swollen and at the end of 24 hours, the circulating blood volume was significantly reduced and the animal entered into a state of shock.

Of particular interest was the fact that local bacterial contamination occurred in each instance in spite of rigid aseptic technique. The crushed muscle at autopsy had a foul odor, gas was often present and smears revealed numerous bacteria of all types including *Clostridium welchii*. It was ascertained by actual measurement that the fluid shift to the traumatized extremity was not sufficient to account for the development of shock.¹⁵ Furthermore, the application of plaster casts to the traumatized limb minimized local accumulation of fluid but did not prevent

the onset of shock.¹⁵ Debridement of the crushed muscle prevented shock when undertaken within 12 hours of the time of operation, but was ineffective when performed after 17 hours. In 50 animals treated with sulfamerazine, shock was prevented in each instance; there was less swelling of the traumatized limb and no significant reduction of the circulating blood volume. When the animals were sacrificed, the crushed muscle at autopsy appeared clean, was free of odor and few or no organisms were found on direct smear. The conclusion was drawn that shock in these experiments was due to systemic absorption of toxic products from the infected muscle tissue.

In subsequent experiments⁹ it was found that sulfamerazine was completely effective in preventing shock if given up to 6 hours after the muscle-crushing operation, slightly beneficial if administered at the end of 17 hours, but without value if withheld for 24 hours. When this drug was applied locally to the crushed muscle, and none administered in any other way, the protective effect was variable, since shock occurred in 2 of 11 animals treated in this manner. In further experiments with the parenteral administration of this agent, it was found that the traumatized muscle contained a much higher concentration of the drug than did the blood or uninjured muscle of the same animal.

* The work described in this paper was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the Mount Zion Hospital.

† The bacteriologic aspect of this project was conducted in collaboration with Dr. Karl F. Meyer, Hooper Foundation, San Francisco.

The experiments described in previous reports from this laboratory^{9,15} are concerned chiefly with the treatment of toxic (infectious) shock with sulfamerazine. Because of the demonstrated potency of penicillin as a bacteriostatic agent, it was considered important to test the action of this drug in this type of shock. It is the purpose of this communication (a) to compare the effectiveness of penicillin and sulfamerazine in preventing shock due to muscle crushing, when these agents are given locally or systemically, and (b) to compare the respective ability of penicillin and sulfonamides to penetrate ischemic, crushed muscle, when these agents are administered intravenously, and (c) to discuss the treatment of shock resulting from wounds involving extensive damage to tissues.

Methods. *Technique of Muscle-crushing Procedure.* The quadriceps femoris of dogs anesthetized with sodium pentobarbital was removed from one hind limb under sterile technique. The muscle was cut into fine pieces, ground in a sterile mortar and then replaced in its original bed, after which the incision was closed. The amount of muscle crushed corresponded to 3 to 5 gm. per kg. body weight.

Plasma Volumes. Estimations were made according to the method of Gregersen and Gibson,^{10,13} employing the blue dye T-1824. The concentration of dye in plasma was determined by means of the Evelyn photoelectric colorimeter.^{5,11}

Penicillin Determinations. The methods of determining the concentration of penicillin in the blood and muscle will be described under the appropriate experiment.

EXPERIMENT 1. *The Parenteral Administration of Penicillin.* The following experiment was performed to ascertain the effectiveness of penicillin, systemically administered, in preventing and counteracting shock due to muscle crushing. The muscle crushing procedure was performed on 8 dogs, weighing 9.1 to 12.7 kg. A series of intramuscular injections of sodium penicillin (5000 Oxford units) was begun in each animal within 15 minutes after operation and continued every 3 hours for 36 hours.

Of the 8 dogs, all but 2 developed shock

within 12 to 24 hours after operation, and all but 1 recovered. The animals were sacrificed when it became evident that satisfactory recovery had taken place. The wounds at autopsy in all but the fatal case appeared clean and free of odor, although cultures of the crushed muscle yielded several types of bacteria, including *Cl. welchii* and *Streptococcus viridans*. A decrease in plasma volume was observed in each of the 6 dogs which developed shock, the greatest reduction having been noted in the animal that died, in which instance the value fell to 41% of the normal. The traumatized leg in the fatal case was greatly swollen and at autopsy the wound was filled with gas, hemolyzed fluid was present and culture showed gross bacterial invasion.

In a previous paper,⁹ it was reported that all but 2 of 52 dogs subjected to the muscle-crushing procedure developed shock. If the results of treatment with penicillin given systemically are compared with these control findings, it is evident that penicillin was of some benefit, since shock was prevented in 2 of 8 treated animals. When, however, the results with penicillin and sulfamerazine are compared, it is clearly established that penicillin, systemically administered, is inferior to sulfamerazine, which is completely effective in preventing this type of shock.⁹

EXPERIMENT 2. *The Local Use of Penicillin.* The following experiment was performed to ascertain the ability of penicillin, locally administered, to counteract shock due to muscle crushing. Eight dogs were subjected to the muscle-crushing procedure. Before reinsertion, the crushed muscle was thoroughly mixed with an isotonic saline solution of sodium penicillin containing 500 units per cc. No other treatment was administered. The animals were observed for a period of 6 to 8 days and at no time exhibited symptoms of shock. The traumatized legs showed slight to moderate swelling and at autopsy the wounds appeared clean and free of odor.

From this experiment, it is concluded that the local instillation of penicillin is completely effective in preventing this type of shock. In a parallel study,⁹ it was found that the local application of sulfamerazine prevented shock in 9 of the 11 dogs tested. The somewhat less successful results with the local use of sulfamerazine can be explained by the fact that penicillin has been

found to be superior to the sulfonamides in this type of infection.^{1,14}

EXPERIMENT 3. Concentration of Penicillin in Blood and Crushed Muscle. The purpose of the following experiment and the succeeding one was to attempt to explain the results of systemic treatment with penicillin and sulfamerazine by the respective ability of these substances to penetrate and accumulate in the ischemic, crushed muscle. A single, large intravenous dose of sodium penicillin (5000 units per kg. of body weight) was given to 6 dogs immediately after subjecting them to the muscle-crushing operation. Samples of blood and crushed muscle were taken 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, and 5 hours, respectively, after the drug was injected, and the amount of penicillin in each sample determined.

The method of analysis was as follows: The concentration of penicillin in the blood was determined: (a) by comparing the inhibitory effects of 0.1 cc. of blood sample with those of 0.1 cc. of known dilutions of penicillin upon colonies of *Staphylococcus aureus* (Heatley) in agar plates,⁶ and (b) by titrations in broth,¹⁶ using *Strep. hemolyticus* (New York 5 strain) with 1% sheep erythrocytes in beef heart broth media, taking prevention of hemolysis as an end-point. For the titrations in broth, penicillin solutions of 10 units per cc. and 1 unit per cc. were run concurrently as controls. Muscle samples were weighed, cut up into small pieces and ground with fine, washed and fused sea sand, with or without broth. The resulting pastes or masses were centrifuged at 24,000 to 28,000 r.p.m. for 10 to 15 minutes. The supernatant liquids were assayed for penicillin potency directly by the agar cup method.⁶ Broth titrations by Rammelkamp's method¹⁶ were run with samples which were sterilized by filtration. Results were adjusted by dilution factors when broth was added in the grinding process.

It was found that the blood concentration of penicillin fell rapidly after attaining an initially high level (Fig. 1). The curves were similar to those of other investigators.^{3,17} At the end of 1 hour, the average concentration of penicillin in the blood was 6.1 units per cc., but the concentration in the muscle was only 0.6 unit per gm. The highest concentration in any of the individual muscle samples was 1.2 units per gm. and was

reached 2 hours after the drug was administered (Fig. 1).

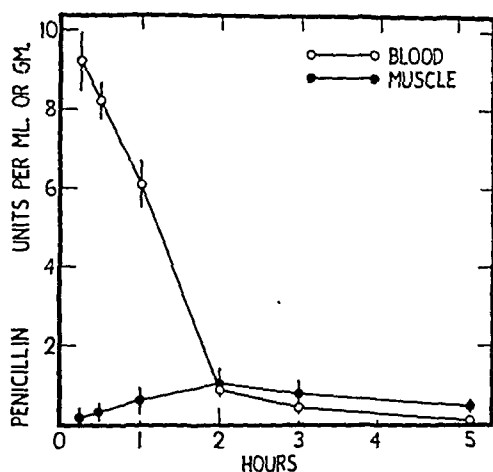


FIG. 1.—Average concentration of penicillin in blood and crushed muscle in 6 dogs after a single, large, intravenous injection (5000 units per kg. body weight). The length of the vertical lines at each point is equal to $2 \times$ the standard deviation of a single observation. The concentration of penicillin in the blood fell rapidly after the initial high level. The maximum concentration in the crushed muscle (1.2 units per gm.) was attained 2 hours after injection.

The failure to achieve a satisfactory concentration of penicillin in the traumatized area after injection in amounts yielding an adequate blood level explains the inability of this agent to be fully effective after parenteral administration. This experiment does not exclude the possibility that if a high blood level of penicillin could be maintained over an adequate period of time, the drug would eventually accumulate in the ischemic, crushed muscle in bacteriostatically effective amounts.

EXPERIMENT 4. Concentration of Sulfamerazine in Blood and Crushed Muscle. Four dogs were subjected to the muscle-crushing procedure. Immediately after operation, each animal received a single, large intravenous dose of sodium sulfamerazine (0.2 gm. per kg. of body weight). No subsequent medication was given. At various intervals after the administration of the drug (15 minutes, 6 hours, 24 hours, 54 hours, 78 hours), samples of blood and crushed muscle were taken and the concentration of sulfamerazine in each was determined by a modification of Bratton and Marshall's method.²

It was found that the blood level was

highest at the first determination made 15 minutes after injection, and steadily declined thereafter until none or only a trace was found at the end of 78 hours. The concentration in the crushed muscle was very low at the end of the 15 minute period, rose gradually and reached its peak at the end of 24 hours, at which time the concentration approximated the maximum blood level (34.4 mg. per 100 cc.). After 24 hours, the concentration curve declined slowly and at the end of 78 hours the muscle still contained between 1.5 and 2 mg. per 100 gm. (Fig. 2). It is of interest to note that sulfamerazine attained levels in the muscle as high or higher than in the blood, while penicillin did not.

venous injection a smaller proportion would penetrate the traumatized muscle than in the instance of sulfamerazine. Accordingly, the following experiment was performed. Four dogs were subjected to the muscle-crushing procedure. Immediately after operation, each animal received a single, large, intravenous dose of sulfanilamide (0.2 gm. per kg. of body weight). At various intervals after injection (15 minutes, 6 hours, 24 hours, 54 hours, and 78 hours), samples of blood and crushed muscle were taken and the concentration of sulfanilamide in each sample determined.

It was found that the blood level was highest at the determination made 15 minutes after injection (22.5 mg. per 100 cc.),

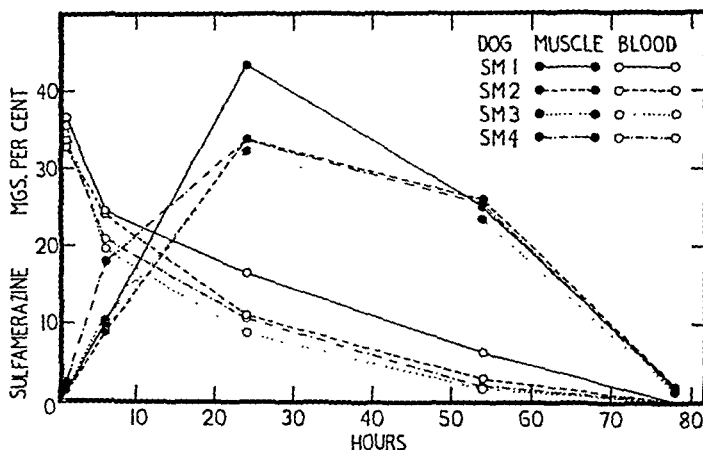


FIG. 2.—Concentration of sulfamerazine in blood and crushed muscle in 4 dogs after a single, large intravenous injection (0.2 gm. per kg. body weight). The blood level was highest at the first determination, 15 minutes after injection, and declined steadily until none or only a trace was found at 78 hours. The concentration in the crushed muscle was very low at the 15 minute period, reached its peak at the end of 24 hours, and then decreased gradually. At the 78 hour determination, the muscle still contained between 1.5 and 2 mg. of sulfamerazine per 100 gm.

According to Fox, sulfonamides circulate in body fluids partly in unionized molecular form, and partly in ionized form. The undissociated form diffuses freely in and out of the tissues, but the ionized sodium salt after entering the traumatized area is bound there like other sodium salts (Fox and Keston⁷). The latter fact helps to explain why sodium sulfamerazine, which is highly ionized at the pH of body fluids (68.5% at pH 7.4¹²), is retained in injured tissues in such large concentrations.

EXPERIMENT 5. Concentration of Sulfanilamide in Blood and Crushed Muscle. Inasmuch as sulfanilamide in solution is almost completely undissociated (99.9% at pH 7.4¹²), it was anticipated that after intra-

and that the concentration curve declined steadily until only traces of the drug were found at the end of 78 hours. The crushed muscle contained only a trace at the 15 minute period. At the end of 6 hours the concentration reached its peak (16.4 mg. per 100 gm.), then gradually decreased until only a trace was present at 78 hours (Fig. 3).

These results indicate that after intravenous injection a smaller concentration of sulfanilamide accumulates in the crushed muscle than in the case of sulfamerazine. This finding confirms Fox's observation⁸ that a drug which is undissociated in the blood would accumulate in injured tissues to a lesser extent than one which is extensively ionized.

Discussion. In previous reports from this laboratory,^{9,15} it was shown in dogs that sodium sulfamerazine, systemically administered, prevented shock produced by a crushing injury to muscle. In these experiments it was found that shock was a direct result of bacterial infection in the traumatized tissue, and the effectiveness of sulfamerazine was attributable to its antibacterial activity. The local application of sodium sulfamerazine was also effective in preventing shock, but not nearly so uniformly as after systemic administration.

its high protein-binding power (80% at pH 7.4¹²). The achievement of sustained high plasma concentrations of this drug helps to explain its prolonged diffusion into the injured area.

Fox and Keston⁷ employed a radioactive isotope of sodium (Na^{24}) to trace the movement of this element in mice subjected to severe injury by burning or tourniquet trauma. Experiments showed that traumatized tissues attracted and retained sodium ions. The amount of sodium retention far exceeded the gain in water (edema), a fact which indicates that

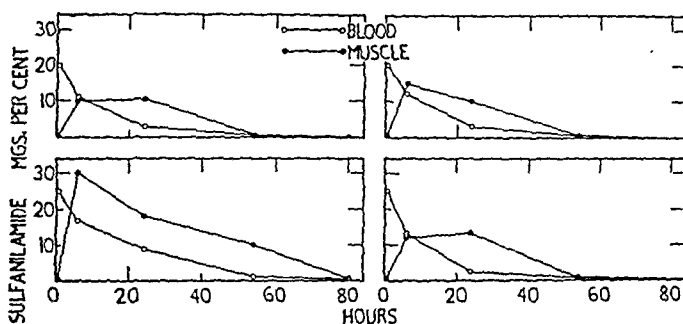


FIG. 3.—Concentration of sulfanilamide in blood and crushed muscle in 4 dogs after a single, large, intravenous injection (0.2 gm. per kg. body weight). The blood level was highest at the first determination 15 minutes after injection, and declined steadily until only traces of the drug were found at the end of 78 hours. The crushed muscle contained only a trace at the end of 15 minutes. The concentration was at the maximum after 6 hours, and declined gradually. At 78 hours, only a trace was present.

In the experiments reported in this paper, sodium penicillin, applied locally to the crushed muscle, was found to be completely effective in preventing the onset of shock, but beneficial only to a variable extent upon parenteral administration.

In an endeavor to explain the results after systemic administration of these drugs, a study was made of their respective penetrability into traumatized, ischemic tissue. Assays of these antibacterial agents in the crushed muscle after intravenous injection, showed that sulfamerazine is readily diffused into the injured tissue in bacteriostatically effective concentration, whereas penicillin is accumulated in mildly inhibitory levels only. Prolonged high levels in the blood are easily attained with sulfamerazine, a fact which appears to be explained by its low excretion rate and

additional sodium accumulated in the intracellular compartment. Administration of isotonic saline solution containing radiosodium was followed by nearly complete retention of sodium in the injured animals and by excretion of sodium in normal controls.

At the hydrogen ion concentration of the blood, sulfamerazine is ionized to a considerable extent (68.5%).¹² The importance of this observation lies in the fact that only the ionized portions of the sulfonamide salts appear to exert antibacterial action.⁸ The undissociated form is distributed with body water and diffuses freely in and out of the tissues like other unionized molecules, *e. g.*, urea and glucose. The ionized form of sulfamerazine upon entering the traumatized area is bound there like other sodium salts, and this fact explains the high concentration of this

chemical in ischemic, crushed muscle after systemic administration.

Sulfanilamide at the hydrogen ion concentration of body fluids is ionized only to the extent of 0.1% and is bound to plasma protein to the extent of 20%,⁴ and as the results of assay show does not accumulate in the blood and traumatized muscle in as high concentration as sulfamerazine.

The low concentration of penicillin attained in traumatized tissue would serve to explain why the systemic administration of this agent is not entirely effective in counteracting shock due to muscle crushing.

The penetration and accumulation of various antibacterial agents into traumatized, ischemic and infected areas is not only of theoretical interest, but is also of obvious practical importance, for this type of injury is a fairly common occurrence not only on the battlefield but also in civilian life.

In treating wounds with antibacterial agents, it is necessary to take several factors into consideration. Drugs should be chosen according to (a) their specificity for the type of bacteria present, and (b) the route of administration, which in turn depends in part upon the blood supply to the wound.

For local therapy, penicillin appears to be superior to sulfamerazine. The local application of penicillin without additional medication prevented shock, whereas the topical administration of sulfamerazine was not entirely effective.

If local therapy is not possible or supplementary systemic treatment seems advisable, the sulfonamide of choice would be one which possesses great bacteriostatic potency, ready diffusibility, and a high coefficient of retention in the blood and injured tissue. Sodium sulfamerazine, a highly ionized salt, was found to fulfill these requirements more satisfactorily than sulfanilamide, an almost wholly undissociated substance. From these observations, it is suggested that an injury involving the crushing of muscle should be treated by administering systemically an

ionized sulfonamide such as sodium sulfamerazine and performing debridement, which as previously stated has been shown to be effective in preventing shock. If in addition the use of a local antibacterial agent is considered desirable, penicillin rather than a sulfonamide would appear to be the drug of choice.

Summary and Conclusions. Muscle crushing experiments were performed in dogs. Shock developed as a result of systemic absorption of toxins from the muscle tissue which became infected in spite of rigid surgical technique. The treatment of shock induced in this manner was investigated by the use of antibacterial agents.

1. The instillation of sodium penicillin at the site of injury was found to be completely effective and superior to the local application of sodium sulfamerazine.

2. The systemic administration of sodium penicillin was shown to be of benefit, but not so uniformly effective as the systemic use of sodium sulfamerazine. This fact is in keeping with the demonstration that given in the manner described penicillin does not penetrate ischemic muscle tissue in amounts that are uniformly bacteriostatic, whereas sodium sulfamerazine does.

3. Sodium sulfamerazine, intravenously injected, penetrates into ischemic, crushed muscle tissue in larger amounts than sulfanilamide, similarly applied. The difference in the penetrability of these substances is explained by their relative degree of ionization, sodium sulfamerazine being highly ionized at the hydrogen ion concentration of body fluids and sulfanilamide being almost completely undissociated.

4. The treatment of crushing muscle injuries suggested by these observations is immediate systemic injection of an ionized sulfonamide, like sodium sulfamerazine, followed by complete debridement of the wound. These procedures can be supplemented by the local application of an antibacterial agent, and for this purpose sodium penicillin is superior to sodium sulfamerazine.

The authors desire to thank Dr. Charles L. Fox and Dr. Ben Sacks for their valuable aid in the preparation of this paper.

REFERENCES

1. ABRAHAM, E. P., CHAIN, E., FLETCHER, C. M., GARDNER, A. D., HEATLEY, N. G., JENNINGS, M. A., and FLOREY, H. W.: Further Observations on Penicillin, *Lancet*, **2**, 177, 1941.
2. BRATTON, J. C., and MARSHALL, E. K., JR.: New Coupling Component for Sulfanilamide Determination, *J. Biol. Chem.*, **128**, 537, 1939.
3. COOKE, J. V., and GOLDRING, D.: The Concentration of Penicillin in Various Body Fluids During Penicillin Therapy, *J. Am. Med. Assn.*, **127**, 80, 1945.
4. DAVIS, B. D.: Binding of Sulfonamides by Plasma Proteins, *Science*, **95**, 78, 1942.
5. EVELYN, K. A., and CIPRIANI, A. J.: Photoelectric Microcolorimeter, *J. Biol. Chem.*, **117**, 365, 1937.
6. FLEMING, A.: In Vitro Tests of Penicillin Potency, *Lancet*, **1**, 732, 1942.
7. FOX, C. L., and KESTON, A. S.: The Mechanism of Shock From Burns and Trauma Traced With Radiosodium, *Surg., Gynec. and Obst.*, **80**, 561, 1945.
8. FOX, C. L., and ROSE, H. M.: Ionization of Sulfonamides, *Proc. Soc. Exp. Biol. and Med.*, **50**, 142, 1942.
9. FREED, S. C., KRUGER, H. E., and PRINZMETAL, M.: Further Observations on the Role of Bacteria in Shock Due to Crushed Muscle in Dogs, *Surgery*, **16**, 914, 1944.
10. GIBSON, J. G., JR., and EVANS, W. A., JR.: Clinical Studies of Blood Volume; Clinical Application of Method Employing Azo Dye "Evans Blue" and Spectrophotometer, *J. Clin. Invest.*, **16**, 301, 1937.
11. GIBSON, J. G., JR., and EVELYN, K. A.: Clinical Studies on Blood Volume: Adaptation of Method to Photoelectric Microcolorimeter, *J. Clin. Invest.*, **17**, 153, 1938.
12. GILLIGAN, D. R.: Blood Levels of Sulfadiazine, Sulfamerazine, Sulfamethazine in Relation to Binding in the Plasma, *J. Pharm. and Exp. Therap.*, **79**, 320, 1943.
13. GREGERSEN, M. I., and GIBSON, J. G., JR.: Conditions Affecting Absorption Spectra of Vital Dyes in Plasma, *Am. J. Physiol.*, **120**, 494, 1937.
14. HOBBS, G. L., MEYER, K., CHAFFEE, E., and DAWSON, M. H.: The Nature and Action of Penicillin, *J. Bact.*, **45**, 65, 1943 (Soc. Proc.).
15. PRINZMETAL, M., FREED, S. C., and KRUGER, H. E.: Pathogenesis and Treatment of Shock Resulting From Crushing of Muscle, *War Med.*, **5**, 74, 1944.
16. RAMMELKAMP, C. H.: A Method for Determining the Concentration of Penicillin in Body Fluids and Exudates, *Proc. Soc. Exp. Biol. and Med.*, **51**, 95, 1942.
17. RAMMELKAMP, C. H., and KEEFER, C. S.: The Absorption, Excretion, and Distribution of Penicillin, *J. Clin. Invest.*, **22**, 425, 1943.

ACUTE PLEURISY AS A DEHYDRATION PHENOMENON IN DIABETIC PRECOMA

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ACUTE dry pleurisy in a known diabetic should be regarded as an infectious pleuritis until proven otherwise. The incidence of respiratory infections including pulmonary tuberculosis is apparently higher in a diabetic person than in the general population.^{1,5} Such infections as a cause of pleurisy in any diabetic patient should be considered before attempting to make other etiologic diagnoses.

We have studied 5 diabetic patients who entered the hospital with uncontrolled diabetes and coexistent acute dry pleurisy. The marked loss of extracellular fluid which occurs in the precoma phase appears to be the chief cause of this phenomenon.

Case Reports. CASE 1. N. G., a 30 year old white male, entered Vanderbilt University Hospital in June, 1944 with a 6 year history of diabetes mellitus. He had been taking 36 units of protamine zinc insulin daily, but had lapsed in his diet and failed to take his insulin regularly.

Six days before admission he grew weak and developed anorexia. Later he noted polyuria and polydipsia. On the day of entry he noted pain in his epigastrium and along both costal margins anteriorly. This pain was greatly aggravated by respiration which "cut off" his breath, and it tended to move to the side on which he would lie. There was no history of cough, hemoptysis, dyspnea, or previous chest pain.

Examination revealed an undernourished, acutely ill man whose breathing was deep and rapid and whose breath smelled of acetone. His temperature was normal. The skin and mucous membranes were very dry. The heart and lungs were normal except for bilateral friction rubs heard low in both

axillæ. The abdomen was moderately rigid with slight epigastric tenderness.

Laboratory studies revealed glycosuria, acetonuria, a red blood cell count of 6.11 million per cmm., 16.5 gm. of hemoglobin per 100 cc., and a white blood cell count of 25,400 per cmm. The blood sugar was 480 mg. %. Blood CO₂ combining power was not determined on admission. Within 14 hours after admission the patient had received 6600 cc. of normal saline solution and 140 units of regular insulin, and was fairly well hydrated. He felt well and no longer complained of abdominal or chest pain. The friction rubs had disappeared. A Roentgen ray examination of the chest showed no abnormalities. An old tuberculin skin test of unknown dilution was positive. The patient was discharged asymptomatic in 2 weeks well regulated on 64 units of globin insulin daily. Nine months later there was no evidence of chest disease.

CASE 2. R. J., a 20 year old college student known to have diabetes for 4 years, entered Vanderbilt University Hospital in August, 1944 in severe diabetic acidosis. He always had been poorly regulated and had been haphazard in his diet and in taking his insulin.

During the week preceding admission polyphagia, polyuria, and polydipsia began. Several urine specimens showed large amounts of sugar. The day before admission he was nauseated, did not eat and did not take his insulin. He became drowsy, and his respirations increased in depth and frequency. He developed severe anterior chest pain which was aggravated by breathing. There were no other respiratory symptoms. A Roentgen ray examination of his chest 1 year previously was negative.

Physical examination revealed an afebrile, but acutely ill, young man, complaining of

severe pain in his chest. There was marked Kussmaul breathing. He was drowsy but could be aroused. His skin was cool and dry, and his face was flushed. Mouth membranes were very dry. Friction rubs were heard low in both axillæ. No râles were heard, and the heart was normal. The blood pressure was 140/80 on entry, but fell to 110/65 within an hour. The abdomen was not tender. The remainder of the examination was not remarkable.

The laboratory examinations included a red blood cell count of 4.89 million per cmm., a hemoglobin of 15 gm. per 100 cc., a white blood cell count of 19,150 per cmm., and urine showing glucose and acetone. The urinary sediment was normal. The blood sugar was more than 400 mg. per 100 cc. Blood CO₂ combining power was not determined.

He was given 5400 cc. of normal saline solution subcutaneously on the night of admission and also 140 units of regular insulin. The stomach was aspirated and lavaged with 5% sodium bicarbonate solution. He improved rapidly on this régime. The following morning, 16 hours after admission, the pleuritic pain and friction rubs had disappeared. A Roentgen ray examination of the chest on this day was negative. An old tuberculin skin test using 0.001 mg., was negative. He was discharged on 36 units of regular insulin and 24 units of protamine zinc insulin. One month later he felt well and had no symptoms of pleuro-pulmonary disease.

CASE 3. C. H., a 21 year old white man, re-entered Vanderbilt University Hospital in June, 1944, with diabetes mellitus of 15 months duration. It had started after an attack of measles with increasing weakness, loss of weight, polydipsia, polyuria, polyphagia and nocturia. He had been regulated on a diet and 40 units of protamine zinc insulin daily.

On the day before admission he felt tired, lost his appetite and noted a slight cold with a nasal discharge. On the morning of admission he vomited twice and soon afterwards was seized suddenly with severe, sharp pain in both costo-vertebral angles which was made much worse by inspiration. The pain was knife-like and cut off his breath; holding his breath made it cease. He had no chills, fever, cough, hemoptysis, dyspnea

or abdominal pain. There was no history of previous chest pain.

Physical examination revealed a somnolent young man in acute respiratory distress complaining of chest pain with each breath. His temperature was normal. There was a strong odor of acetone on his breath, and his breathing was of the Kussmaul type. His skin and oral mucosa were very dry. At both lung bases in the posterior axillary lines scratchy pleural friction rubs were heard. A similar rub was also heard just to the right of the sternum in the fourth interspace anteriorly. The examination of the heart and lungs was otherwise negative. The abdomen was normal.

Laboratory findings included glycosuria and acetonuria. There were 6.3 million red blood cells and 32,500 white blood cells per cmm., and a hemoglobin of 17 gm. per 100 cc. of blood. The blood sugar was 400 mg. per 100 cc. and the blood CO₂ combining power was 30 vol. % 12 hours after admission.

In a period of 15 hours the patient was given 8100 cc. of normal saline solution and 200 units of regular insulin. At this time he was fairly well rehydrated and no longer had chest pain nor audible pleuritic friction rubs. A chest film showed no evidence of pulmonary or pleural disease. Intracutaneous old tuberculin, 0.1 mg., gave a positive reaction. After 2 afebrile weeks he was discharged asymptomatic and well regulated on a diet and 56 units of globin insulin daily. He has not been seen subsequently.

CASE 4. L. I., a 17 year old white female with diabetes of 9 years duration, was admitted to Vanderbilt University Hospital in December, 1940 in diabetic coma with dehydration and acidosis. Symptoms had started 2 days previously when she developed a gastro-intestinal upset coincident with her menstrual period. She became nauseated, did not eat well, omitted 2 doses of insulin, and started to vomit. She became drowsy, developed deep and rapid breathing, and then lapsed into coma a few hours before admission. There were no other respiratory symptoms. No chest pain or recent infections were admitted by the patient later. Previously she had been well controlled on 72 units of protamine zinc insulin and 36 units of regular insulin daily.

On physical examination she was an obese, comatose, very dehydrated young white woman with deep respirations and the odor

of acetone on her breath. At the right lung base posteriorly there was a short friction rub and showers of fine râles on deep inspiration. The remainder of the examination was not remarkable.

Laboratory studies included glycosuria and acetonuria, a blood sugar of 456 mg. per 100 cc. and a blood CO₂ combining power of 16 vol. %. She had a leukocytosis of 21,000, but later the same day and subsequently her white blood cell count varied between 5800 and 7400. A Roentgen ray examination of the chest was negative.

The râles and friction rub disappeared within a few hours after parenteral fluids and insulin were administered. She received 140 units of regular insulin and 60 units of protamine zinc insulin plus 7000 cc. of fluids in the form of saline solution and glucose in saline solution in the first 24 hours, and regained consciousness. She has been followed for more than 3 years with several Roentgen ray examinations of the chest. There has been no evidence of pulmonary tuberculosis. A tuberculin test was not done.

CASE 5. M. M., a 16 year old white girl known to have diabetes for 4 years, entered Vanderbilt University Hospital in January, 1935, complaining of pain in the "side" and drowsiness.

Four days before this admission she developed a cold after exposure to snow and sleet. A little later she noted pain on breathing in the right lower chest which persisted to the time of admission. There was a slight non-productive cough but no chills or fever.

Physical examination showed a drowsy, dehydrated girl with Kussmaul respirations. A friction rub with a few showers of fine râles was present at the right lung base posteriorly; the left chest was clear. She was afebrile.

She had sugar and acetone in her urine. Her blood sugar was 356 mg. per 100 cc., and the blood CO₂ combining power was 15 vol. %. A chest film showed diminished penetration over the left base suggestive of early pneumonia, but the right chest where the abnormal physical findings were noted was entirely clear.

The pleural friction rub disappeared during the first 24 hours of hospitalization after the administration of fluids and insulin. She was followed with numerous chest Roentgen ray examinations after the discharge, and has never developed roentgenologic evi-

dence of pulmonary tuberculosis. She died in 1944 of diabetic coma, staphylococcus septicemia and staphylococcic abscesses of the kidney.

Comment. In all the cases described, the pleuritic pain appeared in known diabetic patients whose disease was out of control. On admission to the hospital, 1 patient was comatose, but the others were drowsy or in the so-called "precoma" state. All showed much dehydration with acidosis and hyperglycemia. In each case the pleural friction rubs were heard by one or more observers.

In the first 2 patients failure to take insulin regularly and to adhere to diets was apparently the cause of the ketosis. The third patient had a cold with rhinitis on the day before admission without other respiratory symptoms. It was thought that this alone could hardly account for his being out of control a day later. The fourth patient presented a more complicated picture in that a gastro-intestinal upset, lapse in diet, failure to take insulin, and a menstrual period occurred at about the same time. This was the only patient to enter the hospital actually unconscious. Later no history of a previous respiratory infection could be elicited. The râles and the friction rub disappeared within a few hours. The râles could have been atelectatic as a postural manifestation following prolonged immobilization of the body in a supine position. After the administration of fluids the leukocyte count quickly dropped to normal, which would also be against an infectious cause of the râles. The fifth patient only gave a definite history of a previous respiratory infection with later development of right pleuritic pain and cough. She had no fever. The friction rub and showers of râles on inspiration were heard at the right base posteriorly. However, the Roentgen ray changes suggestive of early pneumonia were at the left base where there were no abnormal physical findings. If such it was, the left-sided pneumonitis may have helped to precipitate the precomatose state. It was impossible to say that her

acute pleurisy was not infectious in origin, but its rapid disappearance following administration of fluid and insulin was a point in favor of a non-infectious origin.

While at the time of admission it was thought that a respiratory infection was responsible for the acute pleurisy in each case, the clinical courses convinced us that this probably was not true. All patients remained afebrile, and definite evidence of pneumonitis as the cause of pleurisy was lacking. We realize that friction rubs tend to be transient in nature. However, in our series we feel that it was predominantly rehydration which resulted in their rapid and permanent disappearance. All patients were young adults in the age group for tuberculosis with pleurisy and effusion. None of these 5 patients subsequently developed a pleural effusion and in none was there any evidence of active pleuropulmonary disease at later dates.

Regardless of the causes of their diabetes being out of control, the patients were clinically similar in that all were very dehydrated. Within hours after adequate doses of insulin and isotonic saline solution, the patients became more or less fully rehydrated. Coincidentally both the chest pain and the pleural rubs disappeared. The leukocytosis which most showed on admission rapidly disappeared. Subsequently the hyperglycemia and acidosis were controlled within 1 to several days. Chest films failed to show any pulmonary or pleural abnormalities. It is to be emphasized that none of the patients received specific chemotherapy such as sulfonamides.

Discussion. Impending diabetic coma is due to marked changes in the chemical and fluid equilibria of the body and is usually accompanied by many well-known symptoms. Among them may be excessive urine output, deep and rapid respirations, drowsiness, and often nausea, vomiting and abdominal pain. The cause of the abdominal pain has never been fully explained, but Walker⁷ believes that "gastric tetany" from chloride loss due to vomiting

and diuresis may be responsible. There has been nothing reported in the medical literature concerning acute pleurisy in the diabetic precoma state. Marble⁴ states that in a diabetic "any occurrence out of the ordinary should arouse suspicion, and one should instantly investigate any of the following symptoms: headache, anorexia, restlessness, weakness, listlessness, nausea, vomiting, drowsiness, and painful, rapid or deep breathing." There is no elaboration upon the symptom of painful breathing, nor is it stated whether or not it is pleuritic in nature.

Closely linked with changes in the electrolyte balance of the body fluids in diabetes is dehydration. This becomes manifest not only in the circulating fluid but also in the tissues themselves. According to Starling⁶ normally the surfaces of the pleura are kept moist by the secretion of lymph onto their surfaces. It is conceivable that dryness of the pleura could be the main factor in the production of the acute pleurisy seen in these patients.

As polyuria, vomiting and therefore dehydration progress, the blood volume diminishes as reserves of tissue fluids are depleted. With further changes in the electrolyte pattern occurring, the patient may eventually present the picture of peripheral vascular collapse and shock. The blood pressure may be low, the skin may be cool and dry, and the usual moisture of the oral mucosa may be absent. In our patients we believe that the normal amount of lubricating pleural fluid became decreased or absent. Non-diabetic patients that we have seen who were dehydrated because of other conditions such as acute infections or pyloric obstruction did not exhibit friction rubs. The observation, that in the process of being rehydrated by parenteral fluid administration all of our patients soon recovered and the pleural manifestations quickly disappeared, would tend to support our hypothesis.

The location of the friction rubs was quite uniform—low in the chest in the axillary lines where motion between the

visceral and parietal pleural surfaces is greatest.³ Such areas of maximal motion and maximal friction should be the places where friction rubs and pleuritic pain first appear. In our cases the pain was commonly referred anteriorly around the lower rib margins and even to the epigastrium.

We have seen similar precoma patients with abdominal pain which was steady or accentuated by respiratory movements. It is possible that some cases of abdominal pain seen in diabetic acidosis may be referred to the epigastrium from pleural involvement as is often the case in pneumonia. One wonders if dryness of the serous surfaces of the intestines with friction between loops during breathing or from peristalsis could be a contributing cause of the abdominal pain and associated rigidity of the abdominal wall. Rehydration with physiologic saline solution and the administration of insulin in adequate doses tend to abolish these abdominal manifestations quite rapidly.

Experimentally in dogs, Davis² found that marked dehydration produces significant and widespread tissue changes. Most of these were vascular in origin and included the endothelial surfaces of the pleura. The latter became a dull hue and were covered with a layer of fibrin. Often there were subpleural ecchymoses. It is possible that similar changes may occur

in the dehydrated diabetic patient with ketosis. Toxic factors and anoxemia from circulatory failure may be etiologic agents and may contribute to the genesis of these lesions. Certainly the transudation of the liquid elements of the blood through damaged vascular walls onto the pleural surfaces with the deposition of fibrin seems plausible. Such processes along with the generalized dehydration could conceivably account for the production of acute dry pleurisy in our group of patients.

Summary. 1. Five cases of severe uncontrolled diabetes with acute dry pleurisy have been presented.

2. After insulin administration and adequate hydration were accomplished, the pleuritic pain and friction rubs rapidly disappeared.

3. No conclusive evidence of respiratory disease could be demonstrated, and subsequently the patients remained free of pleuropulmonary disease.

4. Marked dehydration from excessive diuresis and vomiting with resulting dryness of the pleural surfaces is thought to play an important rôle in this manifestation.

5. An analogous situation may exist in the production of abdominal pain and rigidity in diabetic acidosis.

6. Other factors including shock and anoxia may contribute to the tissue changes producing pleurisy.

REFERENCES

1. BANYAI, A. L., and CADDEN, A. V.: Diabetes and Tuberculosis, *Arch. Int. Med.*, **74**, 445, 1944.
2. DAVIS, H. A.: Pathology of Dehydration Shock, *Arch. Surg.*, **42**, 939, 1941.
3. Macleod's Physiology in Modern Medicine, edited by P. Bard, 9th ed., St. Louis, C. V. Mosby, p. 550, 1941.
4. MARBLE, A.: in The Treatment of Diabetes Mellitus, by E. P. Joslin, H. F. Root, P. White, and A. Marble, 7th ed., Philadelphia, Lea & Febiger, 1940.
5. ROOT, H. F.: The Association of Diabetes and Tuberculosis, *New England J. Med.*, **210**, 1, 1934.
6. Starling's Principles of Human Physiology, edited by C. E. Evans, 7th ed., Philadelphia, Lea & Febiger, p. 550, 1936.
7. WALKER, H.: The Etiology of Abdominal Pain in Diabetic Acidosis, *Ann. Int. Med.*, **9**, 1178, 1936.

ON THE EXPECTORANT ACTION OF VOLATILE OILS*

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THERE is no more intriguing group of drugs than the class designated as the volatile or essential oils. Most of them have a sensuous appeal, some of them are repugnant, to the senses of smell and taste. Their use in the arts, in commerce and industry, is much more extensive than their use in medicine. Their use undoubtedly extends back beyond the limits of recorded history, for some of them are described in the earliest writings of mankind. Their chemical composition, known in part, still offers a challenge to the efforts of the organic chemist. Their method of formation and their significance in trees and shrubs, in garden plants and in the wild life of the forest and field, offer problems of interest to the plant physiologist. Though many of them have been used in medical practice for thousands of years, we are still largely ignorant of their pharmacologic actions and therapeutic possibilities and continue to wallow in the heritage of dubious, often erroneous, information which has been passed down to us from decades and centuries long since past.

A sub-group of the volatile oils is listed in textbooks of materia medica, pharmacology and therapeutics as having expectorant properties. This group includes a number of volatile oils and their derivatives obtained chiefly from several genera of the coniferæ plus a few medicinal balsams. There are other volatile oils, not ordinarily classified as expectorants, but reported to have expectorant properties, such as oil of eucalyptus.

It was decided to investigate the reputed expectorant action of these drugs by a new method which we have devised and used

successfully in this laboratory for some years.^{3,10} By this technique, bronchial fluid, or what we prefer to call respiratory tract fluid (R.T.F.), is collected through a cannula in the trachea of an animal lightly anesthetized with urethane, under certain standardized conditions. An increase or decrease in the output of R.T.F. is indicative of an altered production or excretion or both of R.T.F., properties which are ordinarily ascribed to expectorant drugs. Using this technique, expectorants such as ammonium chloride, ammonium carbonate, ipecacuanha, guaiacols, creosotes, camphorated tincture of opium, potassium iodide and certain organic iodides, have been found to augment the output of R.T.F. and other expectorant drugs are being studied.

The present report is of a study involving the application of this technique to the reputed expectorant action of several volatile oils and balsams in some 300 animals, including albino rats, guinea pigs, rabbits, cats and dogs.

The drugs used in this investigation have been described in textbooks for so many years, descriptions which have for the most part been copied from one edition or textbook to another, that we have forgotten—or we have never known—when and why they were introduced into therapeutics in the first place. Modern pharmacologic research has ignored them almost entirely. Under these circumstances, some pay little attention to them and some even consider them as useless relics of the past and little, if any, better than placebos. The commercial slogan that it pays to advertise aptly and amply applies in this case—in the negative, as we shall demon-

* This work was aided financially by a grant from the Ella Sachs Plotz Foundation.

strate in the experiments to be described. In the first group of experiments, a series of volatile oils was given by stomach tube in the doses stated to guinea pigs.

Oleum Terebinthinæ, B.P.; *Oleum Terebinthinæ Rectificatum*, U.S.P. XII. Crude turpentine is obtained by tapping trees of various species of the genus *Pinus*. Since it contains resinous and phenolic acids, it is treated with a solution of sodium hydroxide and the rectified oil distilled over. Turpentine was recommended in the Talmud as effective against renal stones.¹⁴ A physician with Columbus on his second voyage to America, described a turpentine as being used by the native Indians.⁸ Flückiger and Hanbury⁶ described various turpentines which were employed by the ancients and note that the Romans found turpentines being used by the peoples in the Alpine regions of Gaul, by the peasants in the Tirol and by the inhabitants of the Swiss Alps. Turpentine has been used, externally and internally, in the treatment of many human ills. Some 2000 years ago, Pliny¹² is stated to have used turpentine internally against cough. But crude turpentine did not become a very popular remedy, for obvious reasons, until about the 17th century when workers in the regions of Bordeaux and Marseilles prepared oil of turpentine by distillation¹² and some time later the process of rectification was introduced. We have found few references to the internal use of oil of turpentine in textbooks published up to the latter half of the 19th century, but after that time it may be found reported regularly as an expectorant and recently Goodman and Gilman⁷ have classified it amongst the more commonly used "stimulant" expectorants.

To the varying fortunes of oil of turpentine as an expectorant, may be added the present, as well as past, confusion in descriptions of its mode of action. Some authors, such as Brown,⁵ describe it as a "stimulant" expectorant, tending to stimulate repair of damaged bronchial mucosa and drying up secretions of the respiratory tract. In other textbooks of recent date,

the statement may be found that oil of turpentine augments the output of R.T.F. The only reason we can find for these antithetical assertions, is that they must be based upon clinical observations in different types of patients. No satisfactory, quantitative method for measuring the volume output of R.T.F. appeared before the publication of the method used in this laboratory and briefly described above.

Oil of turpentine and the other volatile oils were administered to guinea pigs by stomach tube in the doses stated, 3 hours after the animals had been arranged for collection of R.T.F. and at a time when the output of R.T.F. had assumed a steady, plateau level. The output of R.T.F. was noted at intervals of half an hour for a period of up to at least 4 hours after giving the drug, and the output expressed as ml. of R.T.F. per kilo body weight of animal per 24 hours. Each dose of each drug was given to 7 to 10 guinea pigs, the results were tabulated and averaged, and, to facilitate presentation of the data, any increase or decrease in the rate of output of R.T.F. each hour after giving the drug was calculated as a percentage of the average output during the 2 hours immediately preceding administration of the drug. Results obtained in this manner from the administration of 10, 50 and 100 mg. per kilo body weight of oil of turpentine to guinea pigs, have been collected in Table 1. It was found that oil of turpentine augmented the rate of output of R.T.F. in this species for a period of 2 hours following all doses and for up to at least 4 hours following the 50 mg. dose. Not only was the effect more prolonged following the 50 mg. dose, but it was also more marked, while the increase was not nearly as marked following the larger, 100 mg. dose. These results indicate that oil of turpentine markedly increases the output of R.T.F. in anesthetized guinea pigs and suggest that it may have useful expectorant properties.

Oleum Abietis, B.P. Closely related in origin to oil of turpentine, is *Oleum Abietis*, B.P., or oil of Siberian Fir, com-

monly called oil of pine. The name oil of pine is somewhat loosely applied to a number of volatile oils, usually prepared by steam distillation, from leaves or needles or cones of various species of *Pinus* and *Abies*. *Oleum pini pumilionis*, or oil of dwarf pine needles, is listed in the U.S.P. XII, and is of this class of volatile oils. Oil of pine contains esters of the alcohol, borneol, in addition to various terpenes, while oil of turpentine consists chiefly of pinenes and camphene. Oil of pine is

effect upon the output of R.T.F. is recorded in Table 1. Oil of pine augmented the output of R.T.F. in a manner somewhat similar to that of oil of turpentine, though on the average the effect was not as striking. As with oil of turpentine, the 10 and 100 mg. doses did not have as marked an expectorant effect as did the 50 mg. dose.

Terebenam, B.P. Terebene is official in the B.P. and while formally official in the U.S.P., it was deleted with the publication

TABLE 1.—THE EFFECT OF EXPECTORANT VOLATILE OILS AND BALSAMS UPON THE OUTPUT OF R.T.F. IN GUINEA PIGS

Drug	Dose (mg. per kilo)	% increase in output of R.T.F.			
		1st hr.	2nd hr.	3rd hr.	4th hr.
Oil of turpentine	10	133	89	-44	-47
	50	160	112	93	141
	100	34	61	11	-11
Oil of pine	10	79	-10	-8	21
	50	34	76	101	-18
	100	-16	42	103	26
Terebene	10	88	53	26	-9
	50	59	32	46	5
	100	27	27	47	20
Terpin hydrate	10	0	16	-21	-5
	50	76	38	17	-9
	100	96	26	52	13
Oil of anise	10	194	211	121	105
	50	552	347	275	211
	100	54	19	8	25
Oil of lemon	10	30	49	49	0
	50	240	15	-9	-21
	100	30	53	50	-15
Oil of eucalyptus . . .	10	48	58	52	14
	50	157	172	114	101
	100	88	31	8	4
Friar's balsam	0.05 ml./kilo	-20	-25	0	-29
	2.5 ml./kilo	32	32	-5	-25
Control: 12% alc. . . .	5 ml./kilo	0	-26	8	22

described, chiefly as an inhalant, in text-books published in the latter half of the last century. Its introduction into therapeutics seems to be related to the belief that some therapeutic virtue lay in having patients with pulmonary tuberculosis live in the region of evergreen forests where they were continuously exposed to inhalation of the coniferous volatile oils.

Oil of pine, in the form of *Oleum Abietis*, B.P., was given by stomach tube to guinea pigs in doses of 10, 50 and 100 mg. per kilo body weight and the mean percentage

of U.S.P. XII. It is prepared by steam-distilling the product resulting from the action of sulphuric acid upon oil of turpentine. It was introduced in the 19th century, apparently with the idea of improving upon the odor and taste of oil of turpentine, which purpose is partially accomplished in terebene. Further justification for its elimination from the U.S.P. is contained in the results obtained in the present work; for, while it did augment the output of R.T.F., the average increases from doses of 10, 50 and 100 mg. per kilo

body weight of guinea pig were not as marked as those obtained from the use of oil of turpentine or of oil of pine. These results are shown in Table 1.

Terpini Hydras, U.S.P. XII. Terpin hydrate is a terpene alcohol of known composition listed officially in the U.S.P. XII but not in the B.P. 1932 nor in subsequent Addenda to the B.P., although a related product, terpineol, which is prepared from terpin hydrate, is described in the Sixth Addendum of the B.P. which became official in 1943. Terpin hydrate may be made from oil of turpentine by the action of nitric acid in the presence of alcohol and water under specified conditions. It is a solid with little or no odor or taste, for which reasons it was apparently introduced toward the end of the 19th century, in the textbooks of which time one may find brief reference to it. Terpin hydrate was given to guinea pigs by stomach tube in doses of 10, 50 and 100 mg. per kilo body weight. As shown in Table 1, it did augment the output of R.T.F., but not to the same extent as did oil of turpentine.

These were the 4 terebinthinate volatile oils and derivatives investigated. It is obvious that, of this group, the most effective in augmenting the output of R.T.F. was the original oil of turpentine. None of the more recent, "improved" forms of oil of turpentine was as powerful an expectorant as was the original volatile oil. If our data may be applied to human therapy, they would suggest that oil of turpentine is the most effective of the terebinthinate expectorants and should be given in doses of about 1 ml. by mouth in the form of capsules or perles or in a highly flavored fluid vehicle. To the physician and medical student, the greatest drawback to an intelligent understanding of drug therapy has been, as it is today, the overwhelmingly lost list of compounds of reputed therapeutic value which are presented. With the fund of medical knowledge continuously increasing, it is obvious that continuous pruning is necessary, but the problem has always been what to take

out and what to leave in. In the case of drug therapy, factual knowledge is unduly lengthened by having to include lists of drugs in different groups, each list of drugs having more or less the same action. The ideal arrangement would be to select one drug which has been scientifically proven to be the best in the group for general purposes, describe it in detail, and add brief notes upon related drugs which may have some particular virtue in specific circumstances. This process of elimination is not an easy one, but it is, or should be, primarily a function of the researcher in pharmacology and therapeutics. In the present investigation, oil of turpentine was found to be the best terebinthinate expectorant, and should this fact be confirmed, it would be described as typical of the group.

Oleum Anisi, B.P., U.S.P. XII. Our attention was directed next to a few other volatile oils with reputed expectorant properties. The first of these, oil of anise, is prepared by steam-distilling dried, ripe aniseed or the corresponding fruit of the star anise. Anise is one of the most ancient of drugs. The small, annual plant from which it is obtained, originally came from Egypt and the Middle East¹² but later was cultivated in various parts of the world. Charlemagne ordered it cultivated upon his imperial farms in 812.⁶ Many of the ancients described it, including Theophrastus, Dioscorides and Pliny. Dioscorides wrote that it sweetened the breath, was diuretic, useful in dropsy, an antidote against various venoms, carminative, effective against leucorrhea, a galactagogue and an aphrodisiac,¹² while Pythagoras recommended that it be held in the left hand as a cure for epilepsy!¹⁴ Little wonder that it was widely sought after—and widely taxed. In 1305, Edward I of England set about to raise funds for repairing London Bridge and levied a tax upon a number of items amongst which was anise,⁶ while Charles I of England put upon it what was then considered a huge tax but would be looked upon as a mere trifle in this modern Taxing Age.

The star anise is of quite different origin.⁶ It comes from a small tree which is native to China and was described in writings of the time of the Sung dynasty. It was introduced into western medicine in the latter 17th century. Exactly when anise was first used as an expectorant, we have been unable to determine, but in a book published in London in 1682,¹ there may be found references to prescriptions containing aniseed and recommended for pleurisy. Oil of anise is present in one of the most effective antitussive drugs which we have today, namely camphorated tincture of opium or paregoric, and it materially contributes to the expectorant properties of that preparation, even though present in only very small amounts.⁴

When given by stomach tube to guinea pigs in doses up to 50 mg. per kilo body weight, oil of anise proved to be the most effective expectorant of all the volatile oils investigated. As shown by the data recorded in Table 1, the rate of output of R.T.F. was increased as much as six fold. Again, a larger dose of 100 mg. per kilo body weight was much less effective than the medium dose of 50 or even the smaller dose of 10 mg. If these data apply to man, they indicate that oil of anise is not being used to the extent that it might be as an expectorant drug.

Oleum Limonis, B.P., U.S.P. XII. The peel of lemons contains numerous cells filled with an essential oil, which is expressed to form medicinal oil of lemon. The lemon tree appears to have been originally native to India and the word, "lemon," is thought to have been derived from "Limu," a Cashmere word.⁶ Lemons were unknown to the Greeks and Romans and were introduced into western medicine and commerce by the Arabians, probably about the 11th or 12th century. Oil of lemon has been used for various purposes in medicine, being used now chiefly as a flavoring agent in syrup of lemon. In the form of hot, sweetened lemonade, it is a household remedy for coughs and colds, and this use, the exact origin of which we

have been unable to trace, suggested to us the inclusion of oil of lemon in our studies.

The average recommended human dose of oil of lemon is of the order of 2 mg. per kilo body weight. The volatile oil was given to guinea pigs by stomach tube in doses of from 10 to 100 mg. per kilo body weight, and the effect upon the output of R.T.F. is summarized in the data presented in Table 1. As may be seen, oil of lemon augmented the output of R.T.F. and the greatest increase followed the administration of the 50 mg. dose.

Oleum Eucalypti, B.P., U.S.P. XII. Oil of eucalyptus is steam-distilled from the fresh leaves of various species of the eucalyptus tree which is native to Australia. Its chief volatile oil is cineol which, under the name of eucalyptol, is official in the B.P. and U.S.P. XII. Oil of eucalyptus was first used as an adulterant of more expensive, similar oils, such as oil of cajuput which was obtained from a tree native to the region of the Dutch East Indies, which was investigated by the Dutch in the early 18th century and shortly afterwards introduced into European medicine for various purposes, amongst them being as a diaphoretic.⁶ One finds little or no reference to oil of eucalyptus in books upon materia medica published before the second half of the 19th century. Wood¹³ states that while attention was drawn to the virtues of oil of eucalyptus as early as 1792, it was neglected until after 1860 when eucalyptus trees were cultivated in and around Paris. About that time, the supply of cinchona bark from South America had become seriously limited and large scale production in the Dutch East Indies was not yet under way. As a result, there was intensive research for a substitute for cinchona alkaloids in the treatment and prevention of malaria, and, amongst other drugs, oil of eucalyptus was tried because, "the freedom of Australia from malarial climatic influences," was attributed to the presence there of eucalyptus trees.¹³ Eucalyptus trees were planted in several malarial districts and it was reported that portions of the Roman

Campagna were made habitable as a result of cultivation of these trees.¹¹ All of this naturally stimulated considerable laboratory and clinical research, as a result of which it was soon recognized that, while oil of eucalyptus was inferior to the cinchona alkaloids as an antimalarial drug, it did possess other therapeutic properties amongst which was listed its value in bronchitis, nasal catarrh, and allied respiratory conditions.¹³

The average recommended dose of oil of eucalyptus in man is of the order of 10 mg. per kilo body weight. The volatile oil was given by stomach tube to guinea pigs in doses of 10, 50 and 100 mg. per kilo body weight and the effect of these doses upon the rate of output of R.T.F. has been summarized in Table 1. Oil of eucalyptus was found to be effective in augmenting the output of R.T.F., the maximal expectorant effect being obtained with the 50 mg. dose.

Tinctura Benzoini Composita, B.P., U.S.P. XII. In addition to the volatile oils, a number of balsams, such as benzoin, storax and tolu, have been used as expectorants. The chemistry of the balsams is complex, but as they may be regarded as resinified volatile oils of a particular type, it was decided to include one preparation, compound tincture of benzoin or Friar's Balsam, which contains the 3 balsams mentioned, in the present series of experiments. This tincture was given by stomach tube to guinea pigs in doses of 0.05 and 2.5 ml. per kilo body weight; as shown by the data recorded in Table 1, it had little if any effect upon the volume output of R.T.F. The preparation now known as compound tincture of benzoin has evolved from a number of combinations of balsams obtained from Central America and the Dutch East Indies and introduced in the 17th century.^{6,9} Most of these preparations were originally used as vulneraries—some were termed traumatic balsam, wound balsam, and so forth—and were given internally for bronchial catarrh and other conditions. One may find the value of balsams taken internally as expectorants questioned upon clinical grounds in text-

books written toward the middle of the 19th century and our experimental results in animals substantiate the view that balsams, in the form of Friar's Balsam, have little or no expectorant action when taken internally. It is possible that they may have some virtue when administered in the form of a steam inhalation and we plan to investigate this experimentally.

Control Animals. In the above experiments, each drug was dissolved or mixed with 60% alcohol in a concentration such that 1 ml. contained the required dose per kilo body weight. Just before administration, the 1 ml. was mixed with 4 ml. of water, making a total volume of 5 ml. per kilo body weight, which was given by stomach tube. Each dose was given to between 7 and 10 guinea pigs and the results averaged. As a control, a similar group of guinea pigs was given 5 ml. of 12% alcohol per kilo body weight by stomach tube. Changes in the rate of output of R.T.F. were calculated as before and the results have been summarized in Table 1. It may be seen that no marked nor consistent effect upon the rate of output of R.T.F. followed administration of this vehicle.

Species Variation. A study of the pharmacologic actions of a drug ordinarily involves first animal experimentation and then clinical trial. From experiments upon animals, we may ordinarily predict with a fair degree of accuracy what the effect will be in man but we can never be entirely certain until the drug has actually been tried out upon the human subject. In general, it is unwise to predict from experiments upon one species of animals what the effect in man will be. However, if similar or almost similar results are obtained in several species of animals, it is much more likely that the same results will be obtained in man. For this reason, we have selected an exemplary volatile oil, oil of eucalyptus, and studied its effects in various doses and in five species of animals, namely albino rats, guinea pigs, rabbits, cats and dogs. The drug was given as described above and each dose was admin-

istered to from 5 to 10 animals. The results were tabulated, averaged and any effect of the oil of eucalyptus calculated as a percentage effect, as described above. These data have been summarized in Table 2. It may be seen that oil of eucalyptus increased the rate of output of R.T.F. in all 5 species, in some more so than in others, as would be expected. The most effective dose was 50 mg. per kilo body weight. From these data, we may conclude with reasonable certainty that oil of eucalyptus, and hence probably the other active volatile oils studied above, is expectorant in mammals and that the expectorant action probably extends also to man.

tration of most substances in R.T.F. is not very high, ordinarily much lower than in plasma, as previously reported by Boyd *et al.*² To overcome these difficulties, R.T.F. was collected and pooled from 5 to 10 animals given a stated dose of the volatile oils noted, and an analysis made of all the R.T.F. put out before, and secondly during the 4 hours immediately after, the giving of the volatile oil. These results have been summarized in Tables 3 and 4. A glance at the data given in these 2 tables will reveal that the several volatile oils in the doses studied had little effect upon the chloride content nor upon the specific gravity of the R.T.F. of the species studied.

TABLE 2.—THE EFFECT OF OIL OF EUCALYPTUS UPON THE OUTPUT OF R.T.F. IN VARIOUS SPECIES

Species	Dose (mg. per kilo)	% increase in output of R.T.F.			
		1st hr.	2nd hr.	3rd hr.	4th hr.
Albino rat	100	62	105	58	-6
Guinea pig	10	48	58	52	14
	50	157	172	114	101
	100	88	31	8	4
Rabbit	10	25	83	10	-14
	50	67	71	21	7
	100	37	14	-7	-8
Cat	10	37	7	14	-11
	50	45	76	86	-3
	100	23	47	33	10
Dog	10	-15	26	51	40
	50	-9	59	58	24
	100	-8	2	-4	-10

The Chloride Content and Specific Gravity of R.T.F. From the data recorded above, we may reasonably conclude that the volatile oils studied act as expectorants and augment the output of R.T.F. In the next series of experiments, we have attempted to ascertain the effect of these volatile oils upon the composition of R.T.F. Since it was not feasible to make a study of all the known physical and chemical properties of R.T.F., we decided to measure only the chloride content and the specific gravity.

The volume of R.T.F. per hour, or even per several hours, is ordinarily insufficient to provide an aliquot large enough for the satisfactory estimation of these properties. Added to this is the fact that the concen-

The Mechanism of Expectorant Action. Finally, an attempt was made to find the mechanism of expectorant action of these volatile oils. Oil of eucalyptus was again used as a typical example of the group and it was given to guinea pigs in a dose of 50 mg. per kilo body weight. Four groups of 10 guinea pigs each were used. The abdomen was opened and the afferent gastric branches of the vagus nerve severed in the animals of 2 groups. A laparotomy was also performed upon the animals of the other 2 groups, the intestines manipulated, but the gastric nerves were not severed. Oil of eucalyptus was then given, after the animals had been arranged for collection of R.T.F. for a period of 3

hours, by stomach tube to 1 group of guinea pigs with the afferent gastric nerves cut and to another group with the afferent gastric nerves intact. The remaining group of guinea pigs with the afferent gastric nerves cut and the group with the afferent gastric nerves intact were given a corresponding volume of 12% alcohol and acted as controls. The volume output of R.T.F. after oil of eucalyptus and the vehicle alone was then calculated as a percentage change from the initial output, as before, and the results are summarized in Table 5.

From the data recorded in Table 5, it may be seen that oil of eucalyptus augmented the volume output of R.T.F. to essentially the same extent in guinea pigs

with the afferent gastric nerves severed as in those with the nerves intact. There were no significant changes in the rate of output of R.T.F. in either of the control groups. These results indicate that oil of eucalyptus, and probably the other expectorant volatile oils, do not augment the volume output of R.T.F. in guinea pigs, and probably in other mammals, by setting up reflexes to the bronchial glands from the stomach. These expectorant volatile oils do not belong to the class of so-called, "reflex expectorants." The most likely explanation of the expectorant action of these volatile oils is that they directly stimulate the secretory cells of the respiratory tract. There are the less likely pos-

TABLE 3.—THE CHLORIDE CONTENT OF RESPIRATORY TRACT FLUID BEFORE AND AFTER ADMINISTRATION OF VOLATILE OILS

Drug	Species	Chloride content (mg. per 100 ml.)			
		Before	After 10 mg. per kilo	After 50 mg. per kilo	After 100 mg. per kilo
Oil of lemon	Guinea pig	36	36	36	
Oil of pine	Guinea pig	28	28	17	29
Oil of turpentine . . .	Guinea pig	34	..	28	40
Oil of anise	Guinea pig	32	25	32	28
	Rabbit	86	86	71	67
Oil of eucalyptus . . .	Rabbit	73	..	68	77
	Cat	76	65	..	47
	Dog	68	74	102	71

TABLE 4.—THE SPECIFIC GRAVITY OF RESPIRATORY TRACT FLUID BEFORE AND AFTER ADMINISTRATION OF VARIOUS DOSES OF VOLATILE OILS

Drug	Species	Specific gravity of R.T.F.			
		Before	After 10 mg. per kilo	After 50 mg. per kilo	After 100 mg. per kilo
Oil of lemon	Guinea pig	1.083	0.998	0.987	1.009
Oil of pine	Guinea pig	1.015	0.991	0.910	0.990
Oil of turpentine . . .	Guinea pig	1.008	..	0.989	1.005
Oil of anise	Guinea pig	1.018	1.007	1.016	0.982
	Rabbit	0.988	0.989	0.975	0.989
Oil of eucalyptus . . .	Rabbit	0.984	..	0.999	0.997
	Cat	0.993	0.997	..	0.996
	Dog	0.998	0.996	0.997	0.989

TABLE 5.—THE EFFECT OF PREVIOUS SECTION OF THE AFFERENT NERVES FROM THE STOMACH UPON THE OUTPUT OF R.T.F. IN GUINEA PIGS GIVEN 50 MG. PER KILO OF OIL OF EUCALYPTUS

Drug	Afferent nerves	% increase in output of R.T.F.			
		1st hr.	2nd hr.	3rd hr.	4th hr.
Oil of eucalyptus	Cut	221	101	-20	-28
	Intact	168	164	82	70
Control: 12% alc. . . .	Cut	38	-14	32	-34
	Intact	15	3	-29	0

sibilities that the expectorant action is mediated through reflexes initiated elsewhere, such as from the respiratory tract itself, or that the volatile oils stimulate the "expectorant center" in the brain.

Summary. Volatile oils and related compounds have been used as expectorants for many years and as the reason for their introduction into therapeutics has been largely forgotten, their history has been reviewed in some detail. When given by stomach tube to guinea pigs, lightly anesthetized with urethane, the volatile oils of turpentine, pine, anise, lemon and eucalyptus and the related drugs terpin hydrate and terebene, were found to increase the volume output of respiratory tract fluid (R.T.F.). Oil of anise proved to be the most effective expectorant of the group and oil of turpentine the most effective terebinthinate volatile oil. The most effective dose was 50 mg. per kilo body

weight. Compound tincture of benzoin, given by stomach tube, had no significant effect upon the volume output of the respiratory tract fluid (R.T.F.). Regarding species variation, oil of eucalyptus, taken as representative of the group, was shown to be expectorant in albino rats, guinea pigs, rabbits, cats and dogs. In a cursory study of the chemical and physical properties of R.T.F., it was found that the expectorant volatile oils had no effect upon the concentration of R.T.F. chloride nor upon its specific gravity. Investigating the mechanism of expectorant action, it was shown that this effect was not influenced by section of the afferent gastric nerves, from which it was concluded that the expectorant volatile oils do not act reflexly from the stomach but probably directly upon the secretory cells of the respiratory tract.

REFERENCES

1. Á MYNFICHT, H.: *Thesaurus et Armamentarium Medico-Chymicum*, trans. by J. Partridge, London, Churchill, 1682.
2. BOYD, E. M., JACKSON, S., MACLACHLAN, M., PALMER, B., STEVENS, M., and WHITTAKER, J.: *J. Biol. Chem.*, **153**, 435, 1944.
3. BOYD, E. M., JACKSON, S., and RONAN, A.: *Am. J. Physiol.*, **138**, 565, 1943.
4. BOYD, E. M., and MACLACHLAN, M. L.: *Canad. Med. Assn. J.*, **50**, 338, 1944.
5. BROWN, C. L.: *J. Am. Med. Assn.*, **109**, 268, 1937.
6. FLÜCKIGER, F. A., and HANBURY, D.: *Pharmacographia: A History of the Principal Drugs of Vegetable Origin*, 2nd ed., London, MacMillan, 1879.
7. GOODMAN, L., and GILMAN, A.: *The Pharmacological Basis of Therapeutics*, New York, Macmillan, 1941.
8. KREMERS, E., and URDANG, G.: *History of Pharmacy*, Philadelphia, Lippincott, 1940.
9. LA WALL, C. H.: *Four Thousand Years of Pharmacy*, Philadelphia, Lippincott, 1927.
10. PERRY, W. F., and BOYD, E. M.: *J. Pharm. and Exp. Ther.*, **73**, 65, 1941.
11. POTTER, S. O. L.: *Handbook of Materia Medica, Pharmacy and Therapeutics*, 3rd ed., Philadelphia, Blakiston, 1891.
12. STILLÉ, A.: *Therapeutics and Materia Medica*, Philadelphia, Henry C. Lea, 1874.
13. WOOD, H. C.: *A Treatise on Therapeutics*, 4th ed., Philadelphia, Lippincott, 1882.
14. WOOTTON, A. C.: *Chronicles of Pharmacy*, London, Macmillan, 1910.

ALTERATIONS IN CAPILLARY PERMEABILITY IN MENINGEAL IRRITATIONS*

AN AID TO DIFFERENTIAL DIAGNOSIS

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AN increase in capillary permeability is one of the basic tenets of the functional pathology of inflammation. As early as the classic experiments of Cohnheim, dyes were used to demonstrate this phenomenon. The introduction of the fluorescein method⁵ has given still more clearly visible evidence of this increased permeability in human beings. A scratch on the skin,⁸ a small furuncle, an inflamed vein—these all lead to markedly increased filtration of fluorescein into the interstitial space. When measured with the dermofluorometer,⁶ such increased filtration may amount to as high as 400% above normal. It was therefore obvious that similar increases in fluorescein content should be present wherever there is increased fluid transudation into body cavities or tissue spaces in inflammatory conditions.

There are several reports in the pediatric literature about the usefulness of fluorescein in the diagnosis of meningeal changes. They are, however, rather limited in scope because of the patient material, which embraces only a few types of cerebrospinal diseases. Furthermore, because of the early date of these investigations, the technical apparatus were not sufficiently perfected to permit exact estimations of the fluorescein level in the spinal fluid. Kafka,⁴ in a continuation of Ehrlich's studies with fluorescein on the flow of the aqueous humor in the eye, studied the questions of the origin and circulation of the spinal fluid. He administered fluorescein orally and took samples of spinal

fluid 48 hours later, and noted the fluorescein content of the spinal fluid to be constant throughout the spinal canal. Jervell³ gave 2 gm. of uranin (sodium fluorescein) by mouth in 74 pediatric cases, and performed lumbar punctures after 3 hours. The fluorescence of the spinal fluid was observed against a black background in daylight. By this rather crude method an increased fluorescein content was noted in 18 cases of "meningitis" not further specified as to origin, in comparison with 56 normal cases. Schoenfeld⁹ obtained dubious results with a similar method in cases of general paresis. Esselbruegge² injected 0.03 gm. of uranin per kg. intramuscularly in children. Examination of lumbar fluid removed 3 hours later enabled him to make a clear-cut differential diagnosis between meningismus and meningitis. He also stated that in poliomyelitis there was no increase in the fluorescein content of the spinal fluid. Bonar and Bailey¹ administered fluorescein intramuscularly to children and observed the spinal fluid against a dark background after varying intervals. They claimed the method was of great aid in diagnosing epidemic cerebrospinal meningitis.

Our own attention was drawn to this subject when we studied the distribution of intravenously injected fluorescein in various parts of the body, and its relation to capillary permeability. The following methods were used to determine the fluorescein content of the spinal fluid and blood.

* Aided by grants from the Council of Pharmacy and Therapeutics of the Am. Med. Assn. and the John and Mary R. Markle Foundation.

Method. Every patient received intravenously 5 cc. of a 5% solution of fluorescein which also contained 5% sodium bicarbonate.* Exactly 1 hour after the intravenous injection, a spinal tap was performed, and 5 cc. of venous blood was taken. Approximately 1.5 cc. of spinal fluid was needed for the test if the fluorophotometer was used; 0.5 cc. if the visual fluorescence comparator⁷ was used. The spinal fluid was then diluted in a proportion of 1 to 10 with distilled water, and the fluorescein content determined. The blood was centrifuged and the plasma diluted 1:100 with distilled water.

A fluorophotometer (Lumetron model, No. 402FF, Photovolt Corp.) was used for the fluorescein determination. The instrument was set at 100 against a standard solution with a fluorescein content of 200 gamma per 1000 cc. The response of the instrument is a straight line in direct proportion to the concentration. The concentration of fluorescein in the spinal fluid can thus be read directly from the calibration of the slide-wire. The plasma concentration is read in the same way.

We are fully aware that the determination of the fluorescein content of the plasma is not quite accurate, since plasma has a fluorescence of its own near sky blue, and this diminishes the fluorescence of fluorescein slightly by shifting it towards blue. This error can be obviated by the use of a blank plasma sample from the same patient, or by employing extraction methods. Such methods were employed only when we needed exact determinations of the fluorescein content of the plasma in connection with other investigations. In the present studies, however, for the purpose of establishing a ratio of plasma:spinal fluid content, we felt that such accuracy was unnecessary, and that simplicity of the method was desirable for usefulness in the clinical laboratory.

When the visual fluorescence comparator is being used, only 5 cc. of the diluted fluids are needed, thus reducing the amount of spinal fluid required. In this instance, a series of increasing dilutions of the standard is kept available for comparison. The concentrations of fluorescein in the spinal fluid and in the blood are thus determined in gamma per 1000 cc., and the absolute values are noted. In order to take into considera-

tion unusually high blood values due to retention in cases with renal damage, the ratio between the blood level and the spinal fluid level was established in each case.

Of 149 patients examined by this method, 45 had no disease involving the cerebrospinal tract. In this "normal" group, the average content of fluorescein in the spinal fluid 1 hour after intravenous injection was 73.2 gamma per 1000 cc. The highest concentration was 400 gamma, and this occurred in the only case exceeding 300 gamma per 1000 cc. The lowest spinal fluid concentration was too low to be determined, and was, therefore, called 0. The average plasma:spinal fluid ratio was 123:1, and the lowest ratio 37:1. Cases in which the spinal fluid content was too low to be determined are excluded from these calculations.

Sixteen cases with cerebral hemorrhage of recent origin showed an average content of fluorescein in the spinal fluid of 73.6 gamma per 1000 cc. The highest concentration in this group was 339 gamma while the lowest was again 0. The average plasma:spinal fluid ratio was 129:1, and the lowest 59:1.

The next group of cases studied comprised 57 patients with either meningovascular or cerebrospinal lues.† This group included cases with high activity, as well as those in the arrested stage. Only those cases were selected in which the diagnosis had previously been established without any doubt. The average fluorescein content in the spinal fluid of these luetic patients was 42.5 gamma per 1000 cc., with the highest being 130 gamma, and the lowest 0 gamma. The average ratio between the plasma and the spinal fluid was 111:1, and the lowest ratio 30:1.

One patient with Froehlich's syndrome was observed in whom the spinal fluid pressure was increased. In this instance, the fluorescein content of the spinal fluid was 180 gamma per 1000 cc., and the plasma:spinal fluid ratio was 43:1.

In 4 cases with meningioma, the average

* Supplied in ampules by C. F. Kirk & Co., New York.

† We are deeply indebted to Dr. Schmitz and Dr. S. Kleiner for permitting us to examine their patients with meningovascular lues at the Manhattan State Hospital.

fluorescein content of the spinal fluid was 170 gamma per 1000 cc.; the highest, 260 gamma; and the lowest, 64 gamma. The plasma:spinal fluid ratio averaged 50:1, while the lowest ratio was 27:1.

The course of meningococcus meningitis was studied in 8 patients. At the height of the disease, the average fluorescein con-

tent of the spinal fluid was 526 gamma per 1000 cc., with the highest being 1000, and the lowest 155 gamma per 1000 cc. During this acute phase, too, the average plasma:spinal fluid ratio was only 16:1, and the lowest 4:1. In the individual cases of meningococcus meningitis, it was noted that the changes in the fluorescein concentration and ratios mirrored strikingly the clinical course, and significantly did so much earlier than did other laboratory tests. This occurred because the fluorescein tests provide an immediate functional estimate of the inflammatory reaction of the meninges, and are, therefore, not subject to a time lag.

Pneumococcus meningitis was studied in

TABLE 1.—FLUORESCHEIN CONTENT IN SPINAL FLUID

Diagnosis	No. cases	Average (gamma per 1000 cc.)	Highest content	Lowest content	Av. ratio plasma spinal fluid	Lowest ratio
Normal	45	73.2	400	0	123:1	37:1
"Normal" with cerebral hemorrhage	16	73.6	339	0	129:1	59:1
Meningovascular and cerebrospinal lues	57	42.5	130	0	111:1	30:1
Meningococcus meningitis	8	439.3	1000	155.0	16:1	4:1
Meningococcus meningitis, recovery	8	171.0	455	52.6	89:1	13:1
Pneumococcus meningitis	1	526.0	8:1	..
Tuberculous meningitis	3	537.0	1000	83.0
Meningioma	4	170.0	260	64.0	50:1	27:1
Severe avitaminosis	2	1330.0	1470	1190.0	3:1	1.5:1
Froehlich's disease	1	180.0	43:1	..

TABLE 2.—PATIENT H. Q. (MENINGOCOCCUS MENINGITIS) SPINAL FLUID

Date	Day of disease	Globulin	Cells	Sugar (mg. %)	Fluorescein (gamma per 1000 cc.)	Ratio of fluorescein plasma spinal fluid
3/ 4/44	1	++++	6072	35	385.0	12.5 1
3/13/44	9	+	39	78	71.5	48 1
3/16/44	12	—	8	65	56.8	59 1

tent of the spinal fluid was 439.3 gamma per 1000 cc., with the highest being 1000, and the lowest 155 gamma per 1000 cc. During this acute phase, too, the average plasma:spinal fluid ratio was only 16:1, and the lowest 4:1. In the individual cases of meningococcus meningitis, it was noted that the changes in the fluorescein concentration and ratios mirrored strikingly the clinical course, and significantly did so much earlier than did other laboratory tests. This occurred because the fluorescein tests provide an immediate functional estimate of the inflammatory reaction of the meninges, and are, therefore, not subject to a time lag.

Table 2 illustrates the course of a typical case of meningococcus meningitis from the acute phase to complete recovery. Studies of the 8 cases in this group during the various stages of the recovery phase revealed an average spinal fluid concentration of fluorescein of 171 gamma per 1000 cc., the highest was 455 gamma, and

1 case. The fluorescein content of the spinal fluid was 526 gamma per 1000 cc., and the plasma:spinal fluid ratio was 8:1.

Our material for the study of tuberculous meningitis was not unequivocal. Three cases were observed of which only 1 was proved by clinical tests as well as autopsy of tuberculous origin. This case had a content of fluorescein in the spinal fluid of 527 gamma per 1000 cc. and a level of 7020 gamma in the plasma. This results in a ratio of 13:1. The second case had a concentration of 1000 gamma fluorescein per 1000 cc. of spinal fluid, while the third with a somewhat doubtful clinical diagnosis of tuberculous meningitis had a content of 83 gamma per 1000 cc. Although it appears highly probable that tuberculous meningitis produces a high permeability, we feel that our data are insufficient to make a definite statement in this direction.

Two cases of severe avitaminosis in alcoholics exhibited a very high content of

fluorescein in the spinal fluid, the average being 1330 gamma per 1000 cc., the highest 1470, and the lowest 1190. The average plasma:spinal fluid ratio was 3:1, the lowest 1.5:1.

Discussion. The results detailed in these studies seem to indicate that the fluorescein test, as described, permits a rapid, simple determination of the presence or absence of bacterial meningitis. Many other conditions, such as cerebral hemorrhage, meningismus, cerebrospinal and meningovascular lues, which even on careful examination could easily be mistaken for meningitis, are clearly distinguishable from acute meningitis, since they do not show the high fluorescein content in the spinal fluid found with meningitis.

Among the "normal" cases, there were 4 with meningismus. Meningismus was also present in 2 patients with cerebral hemorrhage. None of these, however, exhibited an increased fluorescein content, thus enabling the observer to make an immediate differential diagnosis between meningismus and meningitis.

Severe avitaminosis leads to a general increase in capillary permeability, as we were able to show in tests on the skin. It is then only natural that this generalized increase should also lead to an increase in the permeability of the vessels of the meninges, thus giving rise to the results obtained in our cases.

Several other conditions, such as acute encephalitis and poliomyelitis, as well as lymphocytic choriomeningitis, require fur-

ther investigation where such material is available.

Besides being of great value diagnostically, the fluorescein test enables the observer to estimate promptly the success of therapeutic procedures in cases of bacterial meningitis, since there is no time lag such as occurs in the level of protein or cells in the spinal fluid.

Summary. 1. The content of fluorescein in the spinal fluid 1 hour after intravenous injection with 5 cc. of a 5% solution does not exceed 300 gamma per 1000 cc. in a normal individual.

2. With this technique, patients with cerebral hemorrhage have a normal content of fluorescein in the spinal fluid.

3. Meningovascular and cerebrospinal lues also exhibit a normal permeability of the meninges.

4. Cases of meningioma do not show an increase in the fluorescein content in the spinal fluid.

5. Meningococcus meningitis, pneumococcus meningitis, and tuberculous meningitis produce clear-cut increases of the fluorescein content up to 1000 gamma per 1000 cc. The increase parallels closely the clinical course of the patient and seems more indicative of the actual pathology than the usual tests.

6. Severe avitaminosis of the B group also leads to an increase in the capillary permeability of the meninges, with values up to 1330 gamma per 1000 cc.

7. Meningismus does not produce an increased permeability, and thus can immediately be differentiated from meningitis.

REFERENCES

1. BONAR and BAILEY: Diagnostic Value of Sodium Fluorescein in Epidemic Cerebrospinal Meningitis, *Am. J. Dis. Child.*, **40**, 493, 1930.
2. ESSELBRUEGGE, H.: Uranin Test in the Diagnosis of Meningitis, *Monatschr. f. Kinderh.*, **43**, 1, 1929.
3. JERVELL, D. O.: The Permeability of the Meninges to Uranin as a Method in the Diagnosis of Meningitis, *Brit. Med. J.*, **1**, 210, 1925.
4. KAFKA, B.: Researches Concerning the Formation, Circulation, and Function of the Cerebrospinal Fluid, *Ztschr. f. d. ges. Neurol. u. Psychiat.*, **15**, 482, 1913.
5. LANGE, K., and BOYD, L. J.: The Use of the Fluorescein Test for the Diagnosis and Prognosis of Peripheral Vascular Diseases, *Arch. Int. Med.*, **74**, 175, 1944.
6. LANGE, K. L., and KREWER, E. S.: The Dermofluorometer, *J. Lab. and Clin. Med.*, **28**, 1746, 1944.
7. LANGE, K., MATZNER, M. J., and KREWER, E. S.: An Optical Fluorescence Comparator, *J. Lab. and Clin. Med.*, **30**, 627, 1945.
8. NELLER, J. L., and SCHMIDT, E. R.: Wheal Fluorescence: A New Method of Evaluating Peripheral Vascular Diseases, *Ann. Surg.*, **121**, 328, 1945.
9. SCHOENFELD, W.: Researches in the Disappearance of Dyestuffs From the Blood, *Arch. f. Dermat. u. Syph.*, **132**, 162, 1921.

PROGRESS OF MEDICAL SCIENCE THERAPEUTICS

UNDER THE CHARGE OF
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SULFONAMIDE UROLITHIASIS

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(From the Research Laboratories of Merck & Co., Inc., Rahway, N. J.)

Six years have passed since sulfapyridine-induced uroliths were first described in experimental animals. During these years renal lithiasis has been observed to occur in human subjects as a result of sulfonamide therapy, and methods for the prevention and treatment of renal blockage have been reported, but renal complications still constitute a serious hazard in the use of these clinically valuable drugs. It seemed desirable, therefore, to present a review of the salient features of sulfonamide-induced urolithiasis.

This review divides itself with some overlapping into 4 parts, namely, the pathologic picture, the renal excretion of the sulfonamide drugs, the metabolism or detoxication of these drugs, and finally the factors influencing the prevention and control of urolith formation. These phases of the problem are discussed in order in the following paragraphs, but no attempt has been made to adhere to a strictly chronologic sequence, nor has there been any attempt to include all of the many important papers published in this field.

Pathology. In a short note on poisoning in mice due to "prontosil" (a sulfonamide azo dye of unspecified structure), Oakley⁴⁵ described the presence of prontosil crystals in the straight and convoluted tubules and in the urinary bladder. The following year Stewart, Rourke and Allen⁶³ observed the appearance of sulfanilamide crystals in the urine of patients and suggested the possibility of stone formation in the urinary tract, but it was not until sulfapyridine was introduced into therapeutics that renal complications became significant. Antopol and Robinson¹ announced the formation of acetylsulfapyridine uroliths in experimental animals, and this announcement was followed in the same journal by the report of Gross; Cooper and Lewis²⁰ which described similar observations.

Antopol and Robinson² reported that administration of large experimental doses of sulfapyridine in the rat and monkey lead to urolithiasis. The urolith formation was often unilateral, occurring more frequently on the right side. If the ani-

mal was sacrificed 24 hours after administration of the drug, aggregates of the crystals were often found in the ureter, especially at the level of the bony pelvic brim. After 5 to 10 days of feeding, the concretions were frequently found near the ureterovesical junction or at times in the bladder. In the early part of the feeding period, the ureter was dilated and thinned out. Later, it was indurated and, in some instances, markedly hemorrhagic. The kidney became edematous and enlarged. Bloody urine was found within the dilated portion of the renal pelvis and ureter. In some instances, an amorphous aggregate of crystals and fibrin completely filled the renal pelvis and extended upward into the papillary ducts of the kidney. The bladder was often edematous, especially in the region of the trigone.

These authors reported that, microscopically, the kidney revealed degeneration varying from mild to most severe, especially in the proximal convoluted tubules. With larger doses, the proximal and distal convoluted tubules could not be differentiated from each other. The cytoplasm of the cells forming these tubules was coarsely granular and occasionally vacuolated. Hyaline droplet degeneration was rare. The lumina of the tubules contained globoid eosinophilic bodies. The loops of Henle were markedly distended and contained, in addition to a few globular elements similar to those found in the convoluted tubule, a coagulum which was eosinophilic with hematoxylin and eosin, and blue with azocarmine. In some instances the cells lining the parietal layers of Bowman's capsule were covered by cytoplasm in a cuboid form, in which a nucleus was rarely observed; when one was present, the cell closely resembled a cell of the proximal convoluted tubules. These cells stained red with azocarmine, and transitions between these and the globular red-staining bodies found in Bowman's space were noted. Apparently, these are identical with the globoid bodies described in the

tubular lumina. With azocarmine the glomeruli showed marked thickening of the basement membrane of the glomerular tuft. When doses of sulfapyridine insufficient to produce concretions were administered the same degenerative changes were also found, though usually not so pronounced. Following excessive dosage, the glomeruli were markedly distended and contained, in addition to the cell debris, a coagulum similar to that found in the loop of Henle. The corresponding glomerular tufts were compressed, and the capillaries were collapsed and bloodless. The collecting tubules showed only slight to moderate distention. The lumina of the papillary ducts were filled with coagulum, and only a few contained an appreciable number of the globoid bodies described. Other collecting tubules and papillary ducts contained coagulum and fibrin with clefts corresponding to space in which crystals had been present. Many of the tubules contained and were surrounded by a mantle of polymorphonuclear leukocytes, and rarely a foreign body type of giant cell was found between the tubules. Pyelonephritis and purulent periureteritis and peripyelitis were also observed. If the animals were given ample doses over a long period, calcium casts were found in the tubules.

In cases in which calculi were present within the ureter, the ureter and the renal pelvis showed from slight to extremely pronounced edema of the lamina propria, with a moderate diffuse scattering of polymorphonuclear leukocytes. In isolated instances a phlegmon was found. The epithelium for the most part was intact, but an occasional erosion was observed. In those cases in which the renal pelvis was found to be filled with an amorphous collection of fibrin and smaller calculi, the pelvis contained fibrinous material with clear clefts corresponding to spaces in which crystals had been present. In places the transitional epithelium was absent, and in these locations the fibrin rested directly on the lamina propria.

The blood-vessels in these regions showed extreme dilatation.

At times there occurred extremely hemorrhagic ureteritis and pyelitis, far in excess of that which might be expected from the presence of the corresponding calculus. Occasionally, thrombi were encountered in the veins of the kidney. In some instances obliterating lesions were found within lumina of veins which were not in close proximity to any of the inflammatory zones. Intra-ureteral hemorrhage was at times excessive, and in 2 cases the clotted blood caused urinary obstruction. In some instances, after feeding with doses insufficient to produce concretions, the kidneys were edematous and revealed the glomerular and tubular changes described except that no "crystal casts" were found in the tubules. Because of this observation, and because the hemorrhagic reaction may be extreme, the authors concluded that the formation of the urolith may not always be an independent precipitation process, but may, at times, be dependent upon primary degenerative or vascular changes in the kidney.

Upon the introduction of sulfathiazole into the family of sulfonamide drugs, van Dyke and his associates^{47,65,66} compared the toxicity of sulfathiazole and sulfapyridine in mice, rats and monkeys. The principal pathologic change noted in all 3 species was renal damage. When incorporated in the diet of the rat, 1% sulfapyridine was toxic. The animals showed concretions in the bladder, ureters or in the kidney pelvis, usually with hydronephrosis and hydronephrosis. Of the rats receiving 1% sulfathiazole in the diet, 28% showed yellow streaks in the medullae. These authors concluded that sulfathiazole undergoes less conjugation (that is, acetylation) than sulfapyridine, and this observation was confirmed by Long and associates.^{33,34} Although the mouse acetylates little, if any, of the sulfonamide drugs, hematuria and accretions in the bladder were occasionally seen.⁴⁷ Thus, it should be noted that renal complications were

observed in the absence of acetylation. Gross, Cooper and Scott²¹ demonstrated that both sulfamethylthiazole and sulfathiazole cause urolithiasis, and this condition was associated with secondary infection and pyelonephritis which occasionally caused death. A considerable portion of the uroliths was deposited in the renal tubules, sometimes causing urinary block.

Similar pathologic findings were described in due course after the introduction of each new heterocyclic sulfonamide. Crossley and collaborators¹¹ reported their findings on sulfadiazine. Welch and associates⁶⁷ compared sulfadiazine with the more recently introduced sulfamerazine, and Robinson, Siegel and Graessle,⁴⁹ extending the observations of Schmidt *et al.*,^{51,52} reported studies on sulfapyrazine. These authors observed that rats receiving sulfapyrazine or sulfadiazine revealed essentially the same renal pathology, namely, concretions in the kidney pelvis, ureter and bladder with secondary hydronephrosis, pyonephrosis or pyelonephritis.

The possibility, suggested by Antopol and Robinson, that sulfonamide drugs may produce primary changes in the kidney which predispose to concrement formation has been ignored all too frequently. As the urine passes down the tubules, and water and base are reabsorbed from the glomerular filtrate, the urinary pH drops and the sulfonamide concentration increases. The concentration of the particular sulfonamide excretion product may, thus, exceed its solubility, but precipitation will not necessarily always occur. On the contrary, the supersaturated urine may pass out of the urinary tract in a metastable condition. It is a well-known physical chemical fact, however, that the presence of nuclei, upon which crystals may grow, will cause precipitation from supersaturated solutions. Thus, a primary change in the kidney which furnishes a nidus for crystal growth may determine the presence or absence of concrements within the urinary tract. Further, if the primary changes alter

tubular processes, urolithiasis may occur, whereas it would not occur in a normally functioning kidney. In experimental studies of the newer sulfonamide drugs, Antopol and associates^{4,31} emphasized the damage to the tubular epithelium induced by these drugs. Aside from the dilatation of tubules and glomerular spaces and the formation of globoid bodies, they observed severe parenchymatous degeneration of distal convoluted tubules and collecting tubules, with considerable calcification of both of the latter structures. This picture of calcifying nephrosis was seen occasionally after a single injection of sulfathiazole. Hellwig and Reed²⁵ described a case of a fatal anuria following sulfadiazine therapy and reported that the severe degenerative changes observed in the tubules were similar to those seen in mercuric chloride poisoning. These authors proposed that sulfadiazine is a tubular poison, and that the anuria resulted not because of any failure of renal drainage but because of the tubular damage which permitted a free diffusion of the glomerular filtrate water back into the blood. Wright and Kinsey,⁶⁸ in a study of renal complications in a series of human patients who received sulfadiazine, concluded that the drug may produce 2 types of renal complication, one due to mechanical blockage and the other due to a direct damage of the tubular epithelium. Marshall had considered the influence of sulfonamide drugs upon renal function, and long before the observation of urinary concretions, Marshall cautioned against the use of these drugs in the presence of established renal impairment. His fundamental studies on the renal excretion of the sulfonamide drugs are touched upon in the following section.

Renal Excretion. Shortly after sulfanilamide was introduced into experimental therapeutics, Marshall and associates³⁸ described a colorimetric method for the determination of the sulfonamide drugs in body fluids and tissues. Using this rapid and precise method to great advan-

tage, Marshall established the range of therapeutically effective blood concentrations of sulfanilamide. He soon demonstrated³⁷ that the true toxicity of a difficultly absorbed drug cannot be determined by the dose of the drug administered orally, but that the toxicity of the drug can be related to its concentration in the circulating blood.³⁷ His rational approach to chemotherapy, based upon the idea of maintaining therapeutically effective, but toxicologically safe blood levels, was developed by Marshall and, subsequently, by others. It has now become customary, as each new sulfonamide drug is introduced, to define such levels. With the colorimetric method at hand, Marshall and associates³⁶ studied the renal excretion of sulfanilamide in man and the dog. Taking the simultaneously determined creatinine clearance as a measure of the glomerular filtration rate, Marshall found that the sulfanilamide clearance in the dog was only 20 to 30 % of the creatinine clearance. This result indicates that 70 to 80 % of the free sulfanilamide is reabsorbed during the passage of the glomerular filtrate along the tubule. In man, the average sulfanilamide clearance was 18 % of the inulin clearance, indicating that man, like the dog, reabsorbs large amounts of the drug. The authors found that the sulfanilamide clearance was increased with increasing urine flow, and they stated that the clearance of acetylsulfanilamide is greater than that of free sulfanilamide. In a subsequent communication Marshall and Litchfield³⁷ reported that excessive blood concentrations of sulfanilamide depressed the creatinine clearance in the dog.

In the course of a study on the excretion of urea, Nicholes and Herrin⁴⁴ obtained sulfanilamide clearances which led to the same conclusions as those of Marshall *et al.* And, in essential agreement with the previous work, Loomis and associates³⁵ found that the sulfanilamide clearance in the rabbit is 30 to 40 % of the simultaneously determined creatinine and inulin clearances. These authors re-

ported identical clearances for acetylsulfanilamide, creatinine, and concluded that acetylsulfanilamide is not reabsorbed in the tubules, but is excreted solely by glomerular filtration. These authors also concluded that, in the rabbit, the clearances of both free and acetylsulfanilamide are independent of the urine flow. Similar findings were reported by Shannon.¹²

In a study of sulfapyridine clearance in the dog, Marshall³⁷ noted that blood levels of 10 to 16 mg. per 100 cc. (maintained by the intravenous administration of solutions of the sodium salt) did not depress the creatinine clearance. And although blood levels of 38 to 45 mg. per 100 cc. produced a temporary depression, the creatinine clearance returned to normal in the course of the experiment. The clearance of free sulfapyridine was not greatly increased by urine flows of 0.2 to 4 cc. per minute. The clearance was found to be 16 to 39% of the simultaneously determined creatinine clearance. Thus, sulfanilamide and free sulfapyridine are excreted in a similar manner. Both resemble urea, but are reabsorbed to a greater extent in the renal tubules. In contrast with these findings, Marshall observed that acetylsulfapyridine similarly administered produced a marked depression in the creatinine clearance. The clearance did not return to normal within 24 hours, and concretions were found in the renal tubules at autopsy.

In an extensive survey, Shannon and associates¹² reported their studies on the distribution and renal excretion of a large series of sulfonamide drugs in the dog. In their experiments, fasting animals were given water to insure an adequate diuresis and creatinine plus the sulfonamide under investigation were administered subcutaneously in doses sufficient to produce satisfactory blood levels of both substances. Blood and urine samples were then collected and analyzed. The glomerular filtration rate was taken as equal to the mg. of creatinine excreted per minute divided by the plasma creatinine concentration in mg. per cc. The sulfon-

amide data were manipulated as follows: of the plasma concentration, the filterable sulfonamide concentration in mg. per cc. was determined. This concentration multiplied by the glomerular filtration rate gives the number of mg. of sulfonamide filtered each minute. The product minus the number of mg. of sulfonamide actually found in the urine equals the amount reabsorbed. The ratio of the amount excreted to the amount filtered yields a figure called the *excretion ratio* which is characteristic of the excretion of the compound by the average nephron under the conditions of the experiment. An excretion ratio of 1 indicates that the renal tubules do not participate in the excretion of the drug. A ratio that falls progressively below 1 indicates a progressively increased reabsorption in the renal tubules. A ratio above 1 indicates tubular secretion, the extent of which is reflected in the magnitude of the excretion ratio.

The data in Table 1, taken from Shannon,¹² indicates that sulfapyridine, sulfadiazine and sulfamerazine are reabsorbed to a considerable extent, whereas sulfathiazole appear to be excreted by a process which is almost exclusively that of glomerular filtration. The reabsorption is considerable in the case of sulfamerazine and, as in the case of p-aminobenzoic acid, is of an order of magnitude which suggests that reabsorption proceeds as an active tubular process.

In a more recent study Beyer *et al.*⁷ reported the average renal clearance values, corrected for plasma binding, of 4 unconjugated sulfonamides to be 7.1 for sulfamethazine, 9.3 for sulfamerazine, 15.8 for sulfadiazine and 35.4 for sulfathiazole. These workers noted that the administration of sodium bicarbonate increased the urinary pH but also increased the clearance of all of the compounds by interfering with their reabsorption. This effect was most striking in the case of sulfathiazole where reabsorption of the compound in the renal tubule was almost completely inhibited. Thus, the use of sodium bicarbonate to increase the solubility of sulfon-

amide drugs is not without objectionable features, for as the solubility of the drug is increased, the natural tubular reabsorption of the compound is decreased and this latter effect tends to counteract the former. The authors noted that the production of a water diuresis also increased the clearance of each compound but not to so great an extent as followed the administration of sodium bicarbonate. When the plasma level of the sulfonamide was raised through the ordinary therapeutic range, the authors observed a progressive increase in the tubular reabsorption of the compounds with the result that the clearance values did not tend to change with the plasma levels. This observation serves to emphasize the importance of maintaining an optimum blood concentration of the drug.

urolithiasis, it will be desirable to incorporate them into the clearance picture when analytical methods become available.

Metabolism. Following oral administration, the sulfonamide drugs pass, in part, into the portal circulation and reach the liver. Here, they undergo a series of metabolic reactions which determine to a large extent whether or not the products of these reactions will form uroliths. The products of these reactions, which appear in the urine, may be divided into a *relatively water-insoluble* group and a *water-soluble* group.⁵⁵ The former includes those products which may precipitate in the urinary tract, whereas the water-soluble group includes those products which do not form uroliths. Information concerning these detoxication products is, there-

TABLE 1.—EXCRETION RATIO OF THE SULFONAMIDES

Compound	pKa	Sulfonamide Creatinine clearance ratio	% filterable plasma sulfonamide	Excretion ratio
Sulfanilamide	10.43	0.27	90	0.30
p-Aminobenzoic acid	4.68	0.18	93	0.19
Sulfapyridine	8.44	0.38	69	0.55
Sulfathiazole	7.12	0.40	40	1.00
Sulfamethylthiazole	7.80	0.25	23	1.09
Sulfadiazine	6.48	0.27	83	0.33
Sulfamerazine	7.06	0.13	61	0.21
N ₁ -sulfanilamide—acetic acid (NH ₂ C ₆ H ₄ SO ₂ NHCH ₂ COOH)	3.52	1.35	92	1.47

The clearance studies considered in the foregoing paragraphs are fundamental to an understanding of sulfonamide urolith formation. It is evident, however, that the investigators, for good and sufficient reasons, have limited their clearance studies. Usually, conditions were imposed which permitted the study of the free drug uncomplicated by other urinary excretion products. Marshall has considered the clearance of both the free and acetylated forms, but it is not yet possible to consider the complete clearance picture. As shown in the following section, the metabolism of the sulfonamide drugs is quite complex and products other than the free and acetylated drug are eliminated in the urine. Since these additional products are concerned in the etiology of

fore, of fundamental importance in the etiology of sulfonamide urolithiasis.

Within the relatively water-insoluble group are the parent drug, the N₄-acetyl derivatives, hydroxyl derivatives and possibly other as yet uncharacterized urinary excretion products of the sulfonamide drugs. By direct isolation and identification of the urinary product, Marshall^{38,39} and others⁵ demonstrated that the sulfonamide drugs are, in part, excreted unchanged. Antopol and associates³ were able to produce massive precipitation of the unchanged sulfonamide within the urinary tract by means of intravenous administration of the sodium salts of a number of different sulfonamides. More recently Welch⁶⁷ and others²² have observed precipitation of free sulfadiazine

and sulfamerazine in the kidneys of dogs. Thus, the unchanged drug may form the urinary concrement. Marshall^{38,39} and others^{5,48} demonstrated that the sulfonamides, like p-aminobenzoic acid,¹⁰ are acetylated in various animal species, and Harris and Klein²³ described the acetylation of sulfanilamide by liver slices *in vitro*. It has been amply demonstrated that the acetylated derivative of sulfapyridine is more insoluble than the parent drug, and the first sulfonamide uroliths described¹ were composed almost entirely of N₄-acetylsulfapyridine. Many years ago, Schmiedeberg⁵³ reported that aniline is oxidized in the animal organism to yield p-aminophenol. It was reasonable to assume, therefore, that the sulfonamides, which are homologues of aniline, would undergo a similar oxidation. This reasoning led to the search for and the isolation of a hydroxy-sulfapyridine from dog urine,^{56,57} and led more recently to the isolation from rabbit and monkey urine of a hydroxy-sulfaquinoxaline which was shown to be 2-sulfanilamido-3-hydroxy-quinoxaline.⁵⁹ Uroliths composed of the almost pure hydroxysulfaquinoxaline were observed in the rat and monkey. Thus, this group of *relatively water-insoluble* products consists of the parent drug, N₄-acetyl derivative, hydroxyl derivatives* and possibly others as yet uncharacterized excretion products, and any one or mixtures of these may form kidney stones.

The water-soluble group of urinary excretion products has not been investigated as intensively as the previous group, but in view of the direct and inferential evidence accumulated there can be no reasonable doubt of the existence of this important class of excretion products. Schmiedeberg⁵³ demonstrated that the p-aminophenol resulting from the *in vivo* oxidation of aniline was conjugated as an ethereal sulfate, and Külz³⁰ showed

that the p-aminophenol might also be conjugated as a glucuronide. In analogy with this early work, it was logical, following the isolation of the hydroxysulfapyridine, to seek an ethereal sulfate or a glucuronide, and a highly water-soluble hydroxysulfapyridine glucuronide was isolated.^{56,57} Shortly thereafter, Thorpe and Williams⁶⁴ announced the isolation of glucuronides of a hydroxysulfathiazole and a hydroxysulfanilamide. These direct isolation experiments have been substantiated by inferential studies. Assuming, logically, that the urinary output of a hydroxysulfapyridine glucuronide would be reflected in an increased output of urinary glucuronic acid, it was shown that human subjects receiving sulfapyridine excreted large amounts of the drug in this soluble form.⁶⁰ James²⁶ findings indicate that sulfanilamide is oxidized *in vivo* to a phenol and is then conjugated as an ethereal sulfate. Shelswell and Williams⁶² found that 6 to 12% of the sulfanilamide fed to rabbits gives rise to a phenol which is conjugated and excreted as an ethereal sulfate. More recently,⁵⁵ a simple distribution method was introduced for the study of these excretion products and by means of this method it was shown that, of the "free" sulfonamide (*i. e.*, not including acetyl derivatives) found in rat urine, 40% of the sulfapyridine; 10 to 20% of the sulfanilamide, sulfathiazole and sulfamerazine; and 4 to 6% of the sulfadiazine and sulfapyrazine appears in the form of water-soluble metabolites. The occurrence of similar soluble excretion products were detected in the urine of the rat, rabbit, dog, and man following the oral administration of sulfaquinoxaline.⁵⁹ Thus, there can be no reasonable doubt of the existence of this class of water-soluble excretion products.

Since different animal species metabolize a given drug differently, it is important to know how the sulfonamides are

* The bacteriostatic properties of these products are unknown; yet, it would seem important to know if they possess full antibacterial activity. The products are aromatic amines, and as such they diazotize and couple directly. Consequently, they are measured in mixtures together with the parent drug. If they do not possess bacteriostatic properties, analyses of mixtures will give erroneous information.

detoxified in the human subject. Quite recently, Gilligan,¹⁷ studying the urinary output of ethereal sulfate and glucuronic acid following sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine, sulfapyrazine, sulfamerazine, and sulfamethazine, reported that in no case was the ethereal sulfate output augmented by the drug. The urinary glucuronic acid output was not increased following sulfanilamide, sulfadiazine or sulfapyrazine, but the output was greatly increased following sulfapyridine, sulfamerazine, and sulfamethazine. Stoichiometric calculations indicated that 40% of the total sulfapyridine and 68% of the sulfamethazine appeared in the urine as a water-soluble glucuronide.

When as much as 40 to 68% of a sulfonamide drug appears in the urine as as metabolite rather than as the parent drug, one must consider the implications. Quite clearly, distribution studies, and renal clearance studies which are based upon the original drug are not adaptable to metabolites of that drug. Further, the bacteriologic properties of these metabolites should be known because they are measured in current analytical procedure together with the unchanged drug. If the metabolites are devoid of activity, analytical results may be in error by as much as 40 to 68%, and such a discrepancy may have serious consequences. On the other hand, if the water-soluble metabolites retain the antibacterial activity of the parent drug—and unpublished work suggests that the hydroxysulfapyridine glucuronide retains antipneumococcal activity in the mouse—then, they may be particularly effective in the treatment of urinary tract infections because of the absence of urolith formation. Further, the toxicologic properties of these metabolites may be widely different from those of the unchanged drug. Indeed, certain side-reactions, such as methemoglobin formation, may be more readily attributable to metabolic products than to the drug originally administered. Certainly, the existence of a water-soluble group

and a relatively water-insoluble group of urinary excretion products, appears to be clearly implicated in the etiology of sulfonamide urolithiasis.

As noted above, products of the water-soluble group do not form uroliths. Hence, each portion of the drug so excreted, reduces the amount of the drug available for urolith formation, and it was suggested⁴¹ that any means which may be employed to increase the percentage of the drug excreted in a water-soluble form would decrease the probability of urolithiasis. Conversely, any interruption of the chain of metabolic reactions which yield these products increases the amount of the drug to be excreted in some other form. That interruption of this chain of reactions may lead to an increased incidence of urolithiasis was demonstrated by chloroform and phosphorus liver damage in the rat. Graded damage of the liver reduced the urinary output of hydroxysulfapyridine glucuronide, and the incidence of uroliths was increased from 10 to 25 to 60%. More recently, an increased incidence of renal complications was observed in the course of sulfonamide therapy among patients suffering of liver disease.⁴⁶

Factors Influencing the Prevention and Control of Urolith Formation. After Antopol and Robinson¹ announced the formation of acetylsulfapyridine uroliths, there was renewed interest in Marshall's earlier studies³⁶ of the renal clearance of the sulfonamide drugs. The rapid clearance of acetylated sulfapyridine plus the tubular reabsorption of the unchanged drug suggested a mechanism whereby almost pure acetylated sulfapyridine would be precipitated within the urinary tract. If only the acetylation process could be brought under control, the kidney stone problem would be solved.

A solution along these lines was sought by a number of investigators. It was known from the work of Ellinger and Hensel¹⁰ that p-aminobenzoic acid is acetylated in the rabbit, and Sherwin *et al.*^{8,24,43} had considered dietary meas-

ures which increased the output of acetylated p-aminobenzoic acid in experimental animals. Extending this knowledge, Harris and Klein²³ demonstrated the *in vitro* acetylation of sulfanilamide by liver slices, and they reported that the factor limiting the rate of acetylation was the speed of acetate production in the tissue slices. James²⁷ fed sodium acetate, together with sulfanilamide and with sulfapyridine, and noted a decrease in the toxicity of the drugs, but this decreased toxicity cannot be attributed to a decreased acetylation because the mouse, the experimental animal used by James, does not ordinarily acetylate the sulfonamides. Martin and his associates⁴¹ fed a large series of "detoxifying chemicals" to mice receiving doses of sulfanilamide, sulfapyridine and sulfathiazole, and noted that many substances reduce the toxicity of the drugs. Martin⁴² extended this work and found that administration of glucuronic acid completely inhibited acetylation of sulfonamides in the rat. Martin suggested that administration of glucuronic acid, in accordance with the Mass Law of Reaction, drove the *in vivo* detoxication reactions toward the formation of the water-soluble hydroxysulfapyridine glucuronide,^{56,57} and thus decreased the tendency toward urolith formation by reducing the amount of the drug excreted as the insoluble acetylsulfapyridine. It should be noted, however, that the hydroxysulfapyridine glucuronide is not formed unless the sulfapyridine is first oxidized to the hydroxyl derivative.⁶¹ Oral administration of glucuronic acid will not, presumably, accelerate the initial oxidative reaction. After the drug is oxidized, the hydroxysulfapyridine is converted to the glucuronide by way of two 3-carbon moieties³² rather than by way of one 6-carbon glucuronic acid molecule. These observations cast some doubt upon Martin's hypothesis, but there can be no doubt of the possibility, if not indeed the probability of a decreased toxicity brought about by dietary means. The influence of the diet upon the toxicity of drugs, as

well as the converse, namely, the influence of drugs upon the nutritional state of the host are important topics of current interest, but these topics are much too broad to warrant consideration here. It will suffice to suggest that the dietary may prove to be a useful road to the control and prevention of sulfonamide-induced kidney stones, but this interesting avenue of approach awaits further exploration.

In much of the early work there was a tendency to compare new drugs with old. Investigators sought new drugs which would undergo very little acetylation *in vivo*, the assumption being that a lessened degree of acetylation would parallel a lessened incidence of renal complications. For example, Long and his associates^{33,34} extending the work of van Dyke,^{65,66} reported that less of the acetylated drug was found in the urine of rats, monkeys and human subjects after the administration of sulfathiazole than after administration of sulfapyridine. Similarly, Welch and co-workers⁶⁷ found a greater percentage of acetylsulfamerazine than of acetylsulfadiazine in the urine following administration of the 2 parent drugs. Directing his attention to blood concentrations, Welch concluded that the degree of acetylation does fluctuate considerably, but he also concluded that the blood concentrations of acetylated drug remain low because of rapid elimination by the kidneys rather than because of difficulty in the acetylation of the drugs. This entire point of view has given way to a detailed consideration of the solubility properties of newer and more suitable sulfonamide drugs.

The newer drugs, sulfadiazine,^{11,50} sulfamerazine,⁶⁷ sulfapyrazine,⁴⁰ etc., possess interesting solubility characteristics. Unlike sulfapyridine and sulfathiazole, the newer sulfonamides yield acetylated derivatives which are slightly more soluble than the parent drugs. This fact has been excessively stressed. In stressing this fact it is implied that, because of the increased solubility of the acetylated prod-

uct, these drugs will produce a lowered incidence of urolithiasis. The truth is that these new drugs, when properly administered, do yield a lowered incidence of stones, but this cannot be attributed simply to the increased solubility of the acetylated derivative as compared to the parent drug, for, after all, the solubility differences are relatively small. In no case is the solubility of the acetylated product much greater than twice that of the parent drug at the pH of body fluids. If one considers that the acetylated derivatives are not extensively reabsorbed, but tend, rather, to be cleared rapidly in the kidney, this solubility difference grows somewhat in significance, but when one considers that the parent drug, a hydroxyl derivative, the acetylated sulfonamide, or mixtures of these products may be precipitated in the urinary tract, it is clear that the newer sulfonamide drugs do not owe their successful application solely to a slight difference in the solubility of the free and acetylated products.

When acetylsulfapyridine uroliths were first reported, Antopol and Robinson¹ suggested that the administration of large volumes of water caused solution or removal of the stones. This concept has been universally accepted and all workers, both experimental and clinical, require a controlled daily fluid intake. It was but one step from increasing the urine volume to increasing its pH in order to increase the amount of sulfonamide in solution, and thus to reduce the amount of the sulfonamide precipitated in the urinary tract. The full utilization of the pH variable, however, awaited the synthesis of suitable sulfonamide drugs.

Gelmo,¹⁶ who first synthesized sulfanilamide, recognized that this compound was both a weak base and a weak acid, and as such would form relatively water-soluble salts with acids and bases. While these properties were generally known and hydrochlorides and sodium salts had been prepared,^{15,58} Marshall's preparation of the sodium salt of sulfapyridine for therapeutic administration³⁹ appears to

have focused clinical attention upon the salt-forming properties of the sulfonamide drugs. Since it is possible to form water-soluble sodium salts for parenteral administration, it is also possible to dissolve uroliths by administering alkali. Reasoning thus, Kawaichi and Barnes²⁹ recommended alkali therapy in the treatment of renal lithiasis resulting from sulfonamide drugs, and Climenko and Barlow⁹ reported that renal impairment induced in the monkey by sulfathiazole could be prevented by the administration of sodium bicarbonate, and Schwartz *et al.*⁵⁴ considered the effect of alkali on the crystalluria produced by sulfathiazole and sulfadiazine.

It was not, however, until the newer sulfonamide drugs were synthesized that alkali therapy was placed upon a quantitative basis. Bell and Roblin,⁶ in a fine theoretical paper, reported the anionic dissociation constants of a large series of sulfonamide drugs. These constants qualitatively express the relative solubilities of the drugs at a fixed temperature and at a pH fixed within the range of anionic dissociation. They also indicate to what degree the solubility of a given sulfonamide may be expected to increase with increasing pH increments. Fox¹³ measured the solubility of sulfonamide drugs in a series of buffers, and in conjunction with others,^{14,28} discussed the prevention of renal obstruction by alkali therapy. Similar studies were reported by Gilligan and others.^{18,19} In general, these studies are based upon simple pH-solubility relationships. The salient features of these relationships are illustrated in Figure 1.

Curves 1 and 2 may be taken to indicate the type of solubility data obtained with 2 different classes of sulfonamide drugs. The first class includes sulfanilamide, sulfapyridine and sulfathiazole. The second includes the newer drugs such as sulfadiazine, sulfamerazine, sulfapyrazine, etc. As shown in Figure 1, the solubility of the drugs in both classes increases with increasing pH, but the solubility characteristics of the 2 kinds of drugs differ in one very important aspect. The solubility of

drugs in the first group is not greatly enhanced with increasing pH unless the alkalinity exceeds the physiologic range. These drugs undergo some slight dissociation as acids at the pH of body fluids and alkali therapy may help to prevent precipitation within the urinary tract, more particularly in the case of sulfathiazole, but the influence of alkali cannot be great. On the other hand, the solubility of the drugs in the second class is decidedly and favorably influenced by alkali therapy. These drugs undergo a marked increase in solubility with pH increments falling within the physiologic range and precipitation of these drugs within the urinary system can, within limits, be prevented by increasing the alkalinity of the urine.

possesses a concentration and pH indicated by *A*, precipitation may be anticipated. If, however, alkali is administered together with the sulfonamide and the pH of the urine is increased to *B*, the sulfonamide concentration remaining as before, precipitation may or may not occur. If the drug is a member of the second class, point *B* will fall below the solubility Curve 2. In other words, the urine is not saturated, and precipitation will not occur. But if the drug in question is a member of the first class, point *B* will remain above the solubility Curve 1. The urine is supersaturated, and in the absence of metastability precipitation will occur.

In the foregoing example only the un-

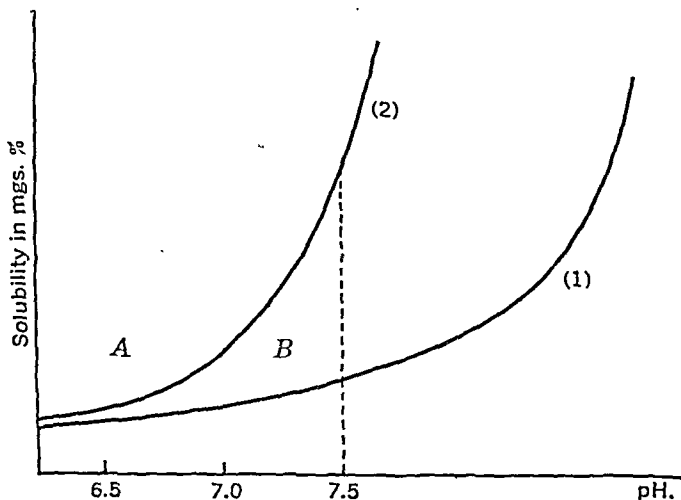


FIG. 1.—pH-solubility relationship of sulfonamide drugs.

An example will serve to illustrate the response of both classes of drugs to alkali therapy. Following medication, the drug is absorbed and a blood concentration is built up. On passing through the glomeruli the unbound drug passes into the protein-free filtrate at a pH of about 7.4. Following the reabsorption of water and base in the tubules, the urinary concentration of the drug may climb as high as 2 to 300 mg. % and the pH may fall as low as 5.5. If the solubility of the drug is exceeded at any point along the way, precipitation may occur. Referring to Figure 1, it is clear that if the urine

changed sulfonamide drug was considered. There is no need to complicate the example by individual consideration of each member of the relatively water-insoluble group of excretion products. In each case the excretion products give rise to similar solubility curves and the same argument holds. This is certainly true of the acetylated sulfonamides, and while no solubility data are available for the hydroxysulfonamides it can be predicted that these substances will yield similar if not more pH-sensitive solubility curves. It may be concluded that with the newer and more acidic sulfonamide drugs, adju-

vant alkali therapy is a powerful aid in the control and prevention of stone formation.

There has been an evident tendency to reason by analogy and to generalize experimental findings in the sulfonamide field. This attitude is usually justified, and in many instances is quite necessary; but analogy and generalization tend to obscure important differences between the individual sulfonamide drugs. Some differences between sulfapyridine, sulfathiazole and sulfadiazine are apparent in the comparative data included in Table 2. The use of adjuvant alkali therapy in the control and prevention of urolithiasis has been considered in preceding paragraphs. It is immediately evident from the data in Table 2, that sulfapyridine will not respond to alkali; sulfathiazole will respond but to a slight degree and

ucts. The metabolism of the sulfonamide drugs was considered in a preceding section where it was pointed out that water-soluble excretion products do not form uroliths, and that each portion of the drug so excreted reduces the amount of the drug available for urolith formation. It appears from the data recorded in Table 2 that the urinary output of such water-soluble products will be an important consideration when sulfapyridine is administered. It may be significant with sulfathiazole but will not be significant when sulfadiazine is administered. These differences, then, are of fundamental importance in the etiology of sulfonamide urolithiasis.

Conclusion. With the newer and more acidic sulfonamide drugs, it has been possible to reduce greatly the incidence of urolithiasis by control of the daily fluid

TABLE 2.—SOME DIFFERENCES IN THE PROPERTIES OF SULFONAMIDES

Drug	pK ^a	Solubility increase produced by increasing pH from 6 to 7.4	Behavior of unchanged drug in renal tubule ¹²	% of urinary products appearing in water-soluble form ¹⁵
Sulfapyridine . . .	8.44	Nil	Reabsorbed	40
Sulfathiazole . . .	7.12	Slight	Not reabsorbed	15
Sulfadiazine . . .	6.48	Marked	Reabsorbed	5

sulfadiazine will respond strikingly to alkali therapy. The renal clearance of various sulfonamide drugs was considered in the preceding section. It will suffice here to point out that the different drugs differ in their mode of excretion. The extensive reabsorption of free sulfapyridine and the rapid clearance of acetylsulfapyridine accounts nicely for the fact that the uroliths are composed almost entirely of acetylsulfapyridine. The lack of tubular reabsorption of sulfathiazole suggests that this drug will give rise to concrements consisting of a mixture of unchanged and acetylated sulfathiazole. The extensive reabsorption of sulfadiazine reduces the urinary output of the unchanged drug and, depending on the relative concentrations of free and acetylated sulfadiazine, precipitation in acidic urine may produce concrements of one or the other or mixtures of both excretion prod-

output and by adjuvant alkali therapy; but other factors and measures are important. Because an established renal or hepatic dysfunction may predispose to sulfonamide urolith formation, these conditions should be considered in conjunction with the administration of the sulfonamide drugs. Perhaps most important in the control and prevention of sulfonamide urolithiasis is strict attention to the blood concentration of the drug. Therapeutically effective, but toxicologically safe, blood concentrations should be maintained throughout the course of therapy. It remains for the clinician to maintain these blood levels by appropriate dosage and adequate diuresis, for as Marshall states, the dose and "the efficiency of the kidneys in excreting the drug . . . are the most important of these factors for the human subject."

REFERENCES

1. ANTOPOL, W., and ROBINSON, H.: *Proc. Soc. Exp. Biol. Med.*, **40**, 428, 1939.
2. ANTOPOL, W., and ROBINSON, H.: *Arch. Path.*, **29**, 67, 1940.
3. ANTOPOL, W., LEHR, D., CHURG, J., and SPRINZ, H.: *Arch. Path.*, **31**, 592, 1941.
4. ANTOPOL, W.: *Arch. Path.*, **30**, 385, 1940.
5. BAINES, E. J., and WEIN, R.: *Quart. J. Pharm. and Pharmacol.*, **12**, 4, 1939.
6. BELL, P. H., and ROBLIN, R. O., JR.: *J. Am. Chem. Soc.*, **64**, 2905, 1942.
7. BEYER, K. H., PETERS, L., PATCH, E. A., and RUSSO, H. F.: *J. Pharmacol.*, **82**, 239, 1944.
8. CERECEDO, L. R., and SHERWIN, C. P.: *J. Biol. Chem.*, **59**, 215, 1923.
9. CLIMENKO, D. R., and BARLOW, O. W.: *Lancet*, **240**, 770, 1941.
10. ELLINGER, A., and HENSEL, M.: *Ztschr. f. physiol. Chem.*, **81**, 21, 1914.
11. FEINSTONE, W. H., WILLIAMS, R. D., WOLFF, R. T., HUNTINGTON, E., and CROSSLEY, M. L.: *Bull. Johns Hopkins Hosp.*, **67**, 427, 1940.
12. FISHER, S. H., TROAST, L., WATERHOUSE, A., and SHANNON, J. A.: *J. Pharmacol.*, **79**, 373, 1943.
- SHANNON, J. A.: *Ann. New York Acad. Sci.*, **44**, 455, 1943.
13. FOX, C. L.: *Arch. Surg.*, **45**, 754, 1942.
14. FOX, C. L., and JENSEN, O. J.: *J. Am. Med. Assn.*, **121**, 1147, 1943.
15. FULLER, A. T.: *Lancet*, **232**, 194, 1937.
16. GELMO, P.: *J. prakt. Chem.*, **77**, 369, 1908.
17. GILLIGAN, D. R.: *J. Clin. Invest.*, **24**, 301, 1945.
18. GILLIGAN, D. R., GARB, S., and PLUMMER, N.: *Proc. Soc. Exp. Biol. and Med.*, **52**, 248, 1943.
- GILLIGAN, D. R., and PLUMMER, N.: *Proc. Soc. Exp. Biol. and Med.*, **53**, 142, 1943.
19. GILLIGAN, D. R., GARB, S., and WHEELER, C.: *J. Am. Med. Assn.*, **122**, 1160, 1943.
20. GROSS, P., COOPER, F. B., and LEWIS, M.: *Proc. Soc. Exp. Biol. and Med.*, **40**, 448, 1939.
21. GROSS, P., COOPER, F. B., and SCOTT, R. E.: *Urol. Cutan. Rev.*, **44**, 205, 1940.
22. GROSS, P., COOPER, F. B., and HAGAN, M. L.: *Am. J. Clin. Path.*, **11**, 882, 1941.
23. HARRIS, J. S., and KLEIN, J. R.: *J. Biol. Chem.*, **124**, 613, 1938.
24. HARROW, B., POWER, F. M., and SHERWIN, C. P.: *Proc. Soc. Exp. Biol. Med.*, **24**, 422, 1927.
25. HELLWIG, C. A., and REED, H. L.: *J. Am. Med. Assn.*, **119**, 561, 1942.
26. JAMES, G. V.: *Lancet*, **238**, 25, 1940.
27. JAMES, G. V.: *Biochem. J.*, **33**, 1688, 1939.
28. JENSEN, O. J., and FOX, C. L.: *J. Urol.*, **49**, 334, 1943.
29. KAWAICHI, G. K., and BARNES, R. W.: *Urol. Cutan. Rev.*, **45**, 477, 1941.
30. KÜLZ, E.: *Pflüger's Arch.*, **30**, 484, 1883.
31. LEHR, D., and ANTOPOL, W.: *Urol. Cutan. Rev.*, **45**, 545, 1941.
32. LIPSCHITZ, W. L., and BUEIDING, E.: *J. Biol. Chem.*, **129**, 333, 1939.
33. LONG, P. H., HAVILAND, J. W., and EDWARDS, L. B.: *Proc. Soc. Exp. Biol. and Med.*, **43**, 328, 1940.
34. LONG, P. H.: *J. Am. Med. Assn.*, **114**, 870, 1940.
35. LOOMIS, T. A., HUBBARD, R. S., and KOEFF, G. F.: *Am. J. Physiol.*, **139**, 197, 1943.
36. MARSHALL, E. K., JR., EMERSON, K., JR., and CUTTING, W. C.: *J. Pharmacol.*, **61**, 191, 1937.
37. MARSHALL, E. K., JR., and LITCHFIELD, J. T.: *J. Pharmacol.*, **67**, 454, 1939.
38. MARSHALL, E. K., JR., EMERSON, K., JR., and CUTTING, W. C.: *J. Am. Med. Assn.*, **108**, 953, 1937.
39. MARSHALL, E. K., JR., BRATTAN, A. C., and LITCHFIELD, J. T., JR.: *Science*, **88**, 597, 1938.
40. MARSHALL, E. K., JR., CUTTING, W. C., and EMERSON, K., JR.: *J. Am. Med. Assn.*, **110**, 252, 1938.
41. MARTIN, G. J., FISCHER, C. V., and THOMPSON, M. R.: *Arch. Int. Med.*, **69**, 662, 1942.
42. MARTIN, G. J., RENNEBAUM, E. H., and THOMPSON, M. R.: *J. Biol. Chem.*, **139**, 871, 1941.
43. MUENZEN, J. B., CERECEDO, L. R., and SHERWIN, C. P.: *J. Biol. Chem.*, **67**, 469, 1926.
44. NICHOLS, H. J., and HERRIN, R. C.: *Am. J. Physiol.*, **135**, 113, 1941.
45. OAKLEY, C. L.: *Biochem. J.*, **31**, 729, 1937.
46. PETERSON, O. L., DEUTSCH, E., and FINLAND, M.: *Arch. Int. Med.*, **72**, 594, 1943.
47. RAKE, G., VAN DYKE, H. B., CORWIN, W. C., MCKEE, C. M., and GREEP, R. O.: *J. Bact.*, **39**, 45, 1940.
48. RATISH, H. D., BULLOWA, J. G. M., AMES, J. B., and SCUDI, J. V.: *J. Biol. Chem.*, **128**, 279, 1939.
49. ROBINSON, H. J., SIEGEL, H., and GRAESSLE, O. E.: *J. Pharmacol.*, **79**, 354, 1943.
50. ROBLIN, R. O., JR., WILLIAMS, J. H., WINNEK, P. S., and ENGLISH, J. P.: *J. Am. Chem. Soc.*, **62**, 2002, 1940.
51. SCHMIDT, L. H., RUEGSEGG, J. M., SESLER, C. L., and HAMBURGER, M., JR.: *J. Pharmacol.*, **73**, 468, 1941.
52. SCHMIDT, L. H., and SESLER, C. L.: *J. Pharmacol.*, **77**, 277, 1943.
53. SCHMIEDEBERG, O.: *Arch. exp. Path. u. Pharmacol.*, **8**, 1, 1878.
54. SCHWARTZ, L., FLIPPIN, H. F., REINHOLD, J. G., and DOMM, A. H.: *J. Am. Med. Assn.*, **117**, 514, 1941.
55. SCUDI, J. V., and JELINEK, V. C.: *J. Pharmacol.*, **81**, 218, 1944.
56. SCUDI, J. V.: *Science*, **91**, 486, 1940.
57. SCUDI, J. V.: *Proc. Soc. Exp. Biol. Med.*, **55**, 197, 1944.

58. SCUDI, J. V.: J. Am. Chem. Soc., **59**, 1480, 1937; Ind. Engr. Chem. Anal. Edit., **10**, 346, 1938.
59. SCUDI, J. V., and SILBER, R. H.: J. Biol. Chem., **156**, 343, 1944.
60. SCUDI, J. V., RATISH, H. D., and BULLOWA, J. G. M.: Science, **89**, 516, 1939.
61. SCUDI, J. V., and ROBINSON, H. J.: AM. J. MED. SCI., **201**, 711, 1941.
62. SHELSWELL, J., and WILLIAMS, R. T.: Biochem. J., **34**, 528, 1940.
63. STEWART, J. D., ROURKE, G. M., and ALLEN, J. G.: J. Am. Med. Assn., **110**, 1885, 1938.
64. THORPE, W. V., and WILLIAMS, R. T.: Nature, **148**, 686, 1940.
65. VAN DYKE, H. B., GREEP, R. O., RAKE, G., and MCKEE, C. M.: Proc. Soc. Exp. Biol. and Med., **42**, 410, 1939.
66. WALKER, H. A., and VAN DYKE, H. B.: J. Pharmacol., **71**, 138, 1941. VAN DYKE, H. B.: Ann. New York Acad. Sci., **44**, 477, 1943.
67. WELCH, A. D., MATTIS, P. A., LATVEN, A. R., BENSON, W. M., and SHIELDS, E. H.: J. Pharmacol., **77**, 357, 1943.
68. WRIGHT, D. O., and KINSEY, R. E.: J. Am. Med. Assn., **120**, 1351, 1942.

RADIOLOGY

UNDER THE CHARGE OF

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ROENTGENOLOGIC CHANGES OBSERVED IN TROPICAL DISEASES

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MANY of those who were giving serious consideration to the prospect of armed conflict between the United States and Japan anticipated an increase in the incidence of tropical diseases in this country. As was foreseen, large numbers of our military and civil personnel were obliged to enter and remain in areas where these diseases are endemic. Many of them became infected and of these some were returned as invalids, carriers of the diseases, or both. Whether or not this is having a significant effect on the general health of our population is probably not definitely known even in official public health circles; but it is more than probable that the civilian physician will be seeing, now and then at least, patients whose ailments are directly or indirectly related to tropical infection of one kind or another. Defining tropical diseases as those which occur or tend to be more prevalent in tropical and subtropical zones than elsewhere, Garland⁶ made a review of the principal ones likely to turn up in this country at the present time or in the near future. "Before a disease can be diagnosed, it must be thought of;" therefore he stressed the pathologic changes which might be encountered at roentgenologic examinations, but he also made brief comments on their clinical manifestations and on some of their epidemiologic features. The discussion has interest and merit not so much because the facts it relates are new, but because they are related from a new point of view, and will serve to keep the reader mindful

of diagnostic possibilities to which his habits of thinking may not be accustomed.

Malaria, Garland noted, is probably the most important world-wide disease of modern times and was undoubtedly the major medical problem of the second world war. Protean in its clinical manifestations, it can mimic numerous diseases of different organs of the body, and so patients with malaria may be referred for roentgenologic examination of almost any region. Most of the victims know that they have had the disease and are able to recognize many of its diverse manifestations themselves. In others, however, the disease may have gone long unrecognized until they have: (1) atypical fever resembling that of tuberculosis or typhoid fever; (2) delirium or convulsions; (3) abdominal pain, simulating appendicitis, cholecystitis or intestinal obstruction; (4) diarrhea; (5) pulmonary symptoms, such as those of bronchitis and pleuritis; or (6) nephritis, sometimes with hematuria. Garland repeated the well-known clinical aphorism to the effect that malaria should be held suspect in any person returned from the tropics who becomes ill. The diagnosis is made, of course, with the demonstration of the specific Plasmodium in the blood smear.

Malaria is one of the diseases in which enlargement of the spleen frequently occurs. Garland reported on 3 instances in which the correct diagnosis of malaria was first suggested when a notation of splenomegaly was made at roentgenologic examination of the urinary tract. The

patients were aware neither of the infection nor of the enlarged spleen.

When is the spleen to be considered enlarged? There is a normal variation in size in different persons and from time to time in the same person. Estimates of enlargement must be made with these points in mind. Garland expressed the belief that a roentgenologic estimate will inevitably be more accurate than a clinical one, but he also pointed out that a uniform technique of projecting the organ on roentgenograms must be developed and adhered to. He established the normal size of the spleen in healthy young men by examining a series of them in the supine position. The distance between the target of the Roentgen ray tube and the Roentgen ray film was 36 inches (91 cm.). The length of the spleen was measured on a line drawn through its shadow somewhat diagonally between the upper and the lower poles. The breadth was measured on a line drawn at right angles to the line between the poles through the widest portion of the shadow. In normal persons the length varied between 8 and 16 cm.; the breadth between 4 and 9 cm. The average length of the shadow of the spleen was 12 cm., the average breadth was 6 cm. When the shadow of the spleen was obscure or indefinite in outline, which happened in about 15% of the subjects, it was apparently possible to obtain satisfactory measurements after the colon or the stomach had been distended with air or other gas to enhance the contrast between the spleen and these neighboring organs. The fact of splenic enlargement was determined with reasonable certainty when the shadow was more than 17 cm. in length. If the length was within normal limits, splenic enlargement was determined when the breadth was more than 9 cm. On rare occasions the spleen had the shape of an inverted U, and this made the problem of measurement more complex.

Serial roentgenologic examinations of the spleen also were made on a group of men 18 to 45 years of age who had mal-

aria of less than 2 years duration. The size of the spleen was determined readily in 85% of cases. Garland advocated measurements of the kind described whenever exact determinations are considered to be necessary or desirable. Norms like those Garland established for young men should be established also for young women and for other age groups of both sexes, because the question of splenic enlargement is frequently raised in standard medical practice and such data might well prove to be useful.

Hepatomegaly is also observed in malaria, but aside from this and splenomegaly, cerebral calcification is the only pathologic malarial change of special roentgenologic interest. Apparently, cerebral calcification occurs only in malaria of great severity and of long standing, and particularly in that variety of the disease caused by *Plasmodium falciparum*. Garland made roentgenologic examinations of the skull in a small number of cases of cerebral malaria and in a larger number of cases of chronic malaria, none of them of more than 3 years' duration, but failed to find evidence of calcification in any instance. He noted that numerous other calcifying parasitic, inflammatory and degenerative lesions of the intracranial structures would have to be considered in the diagnosis of such calcifications.

Other tropical diseases associated with hepatosplenic enlargement noted by Garland are leptospirosis, African trypanosomiasis and leishmaniasis. Hepatomegaly without enlargement of the spleen is seen with amebiasis and the hepatic distomiasis caused by *Clonorchis sinensis*.

Tropical diseases manifested chiefly by intestinal symptoms and signs are bacillary and amebic dysentery, hookworm disease, strongyloidiasis, ascariasis, less frequently filariasis, schistosomiasis and the intestinal form of distomiasis, especially that caused by *Fasciolopsis buski*.

Bacillary dysentery, caused by one of several species of *Shigella*, is encountered the world over, sporadically and in epi-

demics. Since cases of acute bacillary dysentery are seldom referred for roentgenologic examination of the intestinal tract, the manner in which the pathologic changes of this phase of bacillary dysentery might be reflected in roentgenologic findings is not known. Garland noted that in the chronic stage roentgenologic changes resembling those of idiopathic chronic ulcerative colitis have been reported. A chronic form of bacillary dysentery may occur in the tropics. It must be very rare in temperate latitudes. Numerous attempts have been made to show an etiologic relationship of the *Shigella* organisms to undoubted cases of the disease commonly identified as chronic ulcerative colitis. To my knowledge none of them have been successful. The evidence that has been mustered has been neither consistent nor convincing. In fact, there is reason to doubt the very existence of a chronic form of bacillary colitis which might have a confusing similarity to chronic ulcerative colitis.

Endamæba histolytica causes chronic ulcers in the colon, and amebiasis is encountered with moderate frequency even in temperate latitudes. It is, of course, more prevalent in the tropics than in the temperate zone. Many of our military personnel became infested while in tropical zones, and some of them returned to this country as carriers or with amebic dysentery. The same pathogen causes hepatic and pulmonary abscesses, and less frequently abscesses in the brain and in other internal viscera. These abscesses are sometimes demonstrable by roentgenologic methods. They are identified as amebic in origin only by demonstrating the amebæ in the contents or in the walls.

Garland's résumé of the roentgenologic changes to be noted in the colon in cases of amebic colitis was very brief and not very specific. It indicated that he is not impressed with their importance. Druckmann and Schorr⁴ and Golden and Ducharme⁵ discussed these changes in greater detail in papers specifically devoted to that subject.

The diagnosis of amebic disease of the colon is made when *Endamæba histolytica* or one of its vegetative forms is demonstrated in the stools or in the tissues of the patient. The source of such organisms and vegetative forms is considered to be an intestinal ulcer or lesion. The well-known and widely quoted observations of Craig,³ Faust⁵ and Clark² have provided a good foundation in pathologic anatomy on which to construct a roentgenologic diagnosis of intestinal amebiasis. Their studies and those of others indicate: (1) that amebic lesions may be found in any part of the colon but with greatest frequency in the cecum; (2) that when such lesions are found in more aboral portions of the colon an older and possibly a more extensive cecal lesion is also present; (3) that ileal ulcers of amebic origin occur very rarely, and then usually in the severe, often fatal, cases and in patients with debility of high degree; (4) that amebic lesions have different sizes and shapes, varying from a size too small to be seen with the naked eye, to larger deep and crateriform undermined ulcers or shallow and spreading denudation of the mucous membrane; (5) that amebic ulcers are subject to secondary infection with bacterial organisms; and (6) that the segmental tumefactive granulomatous amebic lesions occur, often in the cecum, but also in the more aboral parts of the large intestine. Golden and Ducharme laid emphasis on the significance of the changes in the cecum, although 5 of their patients had changes elsewhere in the colon and rectum. Druckmann and Schorr recognized 2 types of amebic intestinal involvement: (1) a diffuse type, in which lesions are scattered all over the colon, producing roentgenologic changes which they said are similar to those of chronic ulcerative colitis; (2) a localized type, which is more characteristic and in which the colon is involved more or less segmentally in this order of frequency: cecum, ascending colon and sigmoid colon. The changes described in both papers are essentially the same, and except for

their peculiar distribution in the colon, they are the changes expected to be found in chronic segmental colitis of any etiologic type. The lumen of the portion of intestine involved is narrowed, its length is diminished, and the relief of the mucous membrane exhibits varying degrees of obliteration or distortion. These changes in the pattern of the relief of the mucous membrane signify ulceration; the deformity, narrowing and shortening signify inflammatory change, chiefly in the submucous structures. Evidently pathologico-anatomic change of relatively great magnitude must take place before amebic intestinal disease, or for that matter any kind of intestinal disease, will become manifest at roentgenologic examination of the colon. Pin-point ulcers and other lesions too small to be seen with the naked eye can hardly be expected to give convincing evidence of their existence, for roentgenologic evidence is essentially morphologic in character. Functional intestinal changes, such as local or general hypermotility, segmental irritability and tenderness over a particular intestinal segment may, I grant, be observed with such small lesions as their cause, but unless roentgenologic evidence of true morphologic change can be elicited at the same time, such phenomena must be striking and unequivocal if diagnostic value is to be given them. At the same time it is well known that minute lesions may occasionally give rise to alarming clinical symptoms and signs.

As Golden and Ducharme pointed out, deformity of the cecum without demonstrable evidence of change in the lowermost part of the ileum is the roentgenologic syndrome which makes the observer think specifically of intestinal amebiasis. The deformity may be marked and easily recognized, whether the contrast suspension is given by mouth, as Golden and Ducharme preferred to do, or by enema as Druckmann and Schorr considered preferable. The deformity may also be slight, amounting to little more than a barely perceptible but diffuse diminution

in caliber of the cecal segment. Even minimal deformity will be accompanied by changes in the pattern of the relief of the mucous membrane. The changes are usually in the direction of obliteration, but distortion or more or less marked exaggeration of the relief may also be observed. In my opinion, changes of this low degree could not be elicited in a satisfactory manner with the use of the opaque meal alone. The determination of narrowing of an intestinal segment is essentially a test of its distensibility. This test requires active control of the intraluminal pressure. This is possible with the contrast enema, but not, it seems to me, with the contrast meal. Involvement extending to portions of the large intestine below the cecal level is easier to recognize at roentgenologic examination, simply because the deformity is larger and generally more pronounced. When amebic intestinal disease extends below the level of the hepatic flexure, it tends to have an irregular patchy type of distribution. Sites of preference for the lesions are the dependent portions of the colon. These are the sigmoid, colon and the rectum and the dependent portions of the hepatic and splenic flexures. The literature has references to diffuse and uniform involvement of long stretches of the large intestine, but I have not found descriptions of such involvement which were accompanied by illustrative roentgenograms, so I presume that it is rarely encountered. A confusing situation arises in patients who have other etiologic types of ulcerative colitis, and who are at the same time carriers of *Endamoeba histolytica*. Such cases are probably best classified as instances of mixed infection.

I have described a secondary sign of amebic infection of the cecum which I still consider to be of value.¹¹ Golden and Ducharme seem to have misunderstood the description for they apparently tried to elicit the sign with the use of the contrast meal. The sign consists essentially in an unusually free flow of the contrast enema from the cecum, through

the ileocecal orifice, into the lower part of the ileum. It is almost always possible to make some of the contrast fluid enter and fill the terminal ileum after the cecum has been distended with the fluid, but often a special effort must be made to accomplish this especially in patients who have undergone appendectomy. When ileal filling is accomplished in this way, the ileocecal orifice is said to be patent. When the cecum has undergone even minimal morphologic change as a result of amebic infection, the ileocecal orifice often seems to be gaping rather than merely patent or capable of being forced open by sustained pressure, and the contrast fluid enters the ileum with remarkable ease and in unusual volume. To avoid the use of the word "patent" which had acquired a certain disrepute because clinical symptoms had been erroneously ascribed to so-called incompetency of the ileocecal valve, I used the term "patulous" to describe this condition of the structure. I have used this phenomenon consistently and with satisfaction not as diagnostic evidence of amebic intestinal disease, but as a signal to be on the alert for minimal roentgenologic evidence of morphologic change in the cecum when more obvious evidence was lacking. It is not always to be elicited, but in most of the cases of amebic typhlitis which I personally have observed it has been exhibited, and I have not seen it in connection with other etiologic types of ileocecal disease. I am unable to give an anatomic or physiologic explanation of the phenomenon. Golden and Ducharme observed it only rarely, but they used the contrast meal alone in the large majority of their roentgenologic examinations, although they recommend, as I do, the use of both the contrast meal and the contrast enema as the best roentgenologic approach to the diagnosis of intestinal amebiasis.

In the series of cases analyzed by Golden and Ducharme deformity of the cecum was observed more frequently in patients who had intestinal symptoms than in those

who had no such clinical manifestations. How many of the carriers of *Endamoeba histolytica* will be found to have roentgenologically demonstrable evidence of cecal or intestinal disease? Golden and Ducharme found such evidence in 25 of 58 patients who had the specific parasite in their stools. They concluded that the absence of cecal deformity is of no value in excluding intestinal amebiasis. Patients, however, are referred for roentgenologic examination of the intestine for many reasons and under various circumstances. Specific indications for microscopic examinations of the stools are not always at hand in intestinal amebiasis. Numerous examinations of the stools are often required to discover the organism. Positive roentgenologic findings not infrequently serve to stimulate a more vigorous and determined search for the organisms, or actually initiate the search. This is the real value of the roentgenologic examination of the colon in amebiasis. It may also be used with advantage to check the effects of anti-amebic therapy. Golden and Ducharme observed improvement in the roentgenologic appearance of the cecum in a few of the patients they were able to follow after treatment. In instances of marked cecal deformity, however, little change for the better was observed and they concluded that in later stages the changes produced are probably more or less irreversible. This observation was made also by others who had the opportunity of studying numbers of cases of intestinal amebiasis roentgenologically.

Neither Golden and Ducharme nor Druckmann and Schorr mentioned the contribution of the proctologic examination to the diagnosis of amebiasis. Buie and many others have frequently called attention to the typical morphologic characteristics of amebic ulceration as it appears at endoscopic examination of the rectum and sigmoid colon. The experienced proctologic observer apparently encounters no particular difficulty in making a distinction between amebic and

other etiologic types of proctosigmoiditis. I once made a survey of a series of carriers of *Endamæba histolytica* who came under observation consecutively over a period of several years. More than 50% of these patients had amebic ulcers in the recto-sigmoidal region at proctoscopic examination. A slightly greater percentage of the patients had roentgenologic evidence of amebic intestinal disease. A large majority of the patients who had roentgenologic evidence of the disease also had rectosigmoidal amebic ulcers. Since that time I have held that the proctoscopic examination is almost as valuable an adjunct to the diagnosis of amebiasis as the roentgenologic examination is. This is a somewhat anomalous situation when one considers that the cecum is universally considered to be the site of earliest and probably severest amebic involvement. Apparently the clinical investigation for amebiasis should not be considered complete unless it includes scrupulous search for the organisms in the stools, roentgenologic examination of the colon after the contrast meal and the contrast enema, and proctologic examination, including, when indicated, the removal of a specimen of rectosigmoidal tissue for biopsy.

Gastro-intestinal symptoms of all grades of severity may be observed in hookworm disease, caused usually by *Necator americanus* or *Ancylostoma duodenale*. Hodes and Keefer,⁹ in an excellent paper which may well be long remembered as a classic on this subject, confirmed the earlier observations of Krause and Crilly,¹⁰ who described alterations in motility and pattern of the small intestine similar in almost all respects to those seen in the so-called deficiency states. Hodes and Keefer served in a general hospital of the Army of the United States in the Province of Assam in India where the incidence of hookworm disease is reputedly as high as in any place in the world. Their studies were conducted on military personnel who became infected in that area. The worms are infectious to man in their larval stage. The larvæ burrow through the skin, enter

the veins and lymph vessels and are carried to the heart and lungs. Penetrating the capillary and alveolar walls they get into the bronchi, thence to the epiglottis and then are spilled into the esophagus and swallowed. In the intestine the larvæ develop into mature forms in about 1 month. By means of their mouth capsules they attach themselves to the intestinal mucous membrane whence they are nourished. Their preferred habitat is the duodenum, jejunum and upper part of the ileum. Itching is noticed in the burrowing stage by those infected. The term "ground itch" became a common one among soldiers in endemic areas. Cough, dubbed "foxhole cough" by troops, commonly appeared 1 or 2 weeks after the ground itch. Gastro-intestinal symptoms, appearing in from 6 to 25 weeks after exposure, began with nausea, vomiting, abdominal pain and diarrhea. Fever of low grade, abdominal tenderness, and leukocytosis were observed less frequently. Anemia was infrequent in the patients observed by Hodes and Keefer, but most of them were observed in the relatively early phases of the disease. One hundred and twenty-five American troops with proved ancylostomiasis were examined roentgenologically for gastro-intestinal changes; 60% of them proved to have significant alterations in the small intestine within 1 month after exposure to the parasites. The changes were described in intimate detail by Hodes and Keefer and the description is not easily paraphrased in brief form. Suffice it to say that the changes were analogous to, if not exactly like those seen in some of the cases of chronic avitaminosis and other deficiency states. Golden preferred to call them changes of "disordered motor function." They were characterized by exaggeration of the segmental and peristaltic contractions accompanied by distortion of the pattern of the mucous membrane. The abnormal intestinal picture appeared first in the upper part of the jejunum and spread from there to the lower part of the duodenum, to the rest of the jejunum and

to the entire ileum. Hodes and Keefer discussed the various factors possibly operative in producing the changes. They concluded that the alterations could best be explained by postulating damage to the intramural nervous system of the small intestine. They regarded it as highly possible that the hooklike teeth of the parasites, embedded as they are deep in the mucous membrane of the intestine, could easily interfere with the network of nerve cells and fibers which extend to all portions of the intestine from Auerbach's subserosal, and Meissner's deep muscular plexuses. Because the abnormal appearance of the intestine persisted after the hookworms were destroyed by vermifugation, and because 40% of the patients with known hookworm disease failed to show evidence of intestinal abnormality, it seemed probable that the mere presence of the hookworms should be held responsible for the changes. In some cases the intestinal abnormality persisted for months after the patients were clinically well; in others, improvement was observed to occur early.

According to Garland, ascariasis is the most frequently encountered helminthic infection. The shadows of the worms have been demonstrated at roentgenologic examination of the intestine. They appear as elongated intraluminal shadows corresponding to the size and shape of the worms. Frequently the intestinal tract of the worm is outlined by the contrast material ingested by the worm from the host's intestine. Ascariasis is a diagnosis heretofore but rarely made at roentgenologic examination. It is probable that the incidence of this disease will not increase perceptibly in this country as a result of infestations acquired by our military personnel in foreign fields. Garland stated that the actual incidence of intestinal parasitism was low in naval personnel returning from the Pacific theater in the early years of the war.

Of special roentgenologic interests are the calcifications in the soft tissues of the body caused by parasites, some of which

are strictly tropical in distribution, others observed in more temperate zones but much less frequently. The cerebral calcification occurring in certain cases of chronic malaria has already been mentioned. Diffuse cerebral calcification also may be discovered in cases of toxoplasmosis, caused by the sporozoan *Toxoplasma*, especially in case of the infantile type. The symptoms are those of encephalomyelitis. According to Garland, the calcified masses are usually bilateral, 1 to 3 mm. in diameter, and located in the cerebral hemispheres. Curvilinear streaks of calcification sometimes appear in the basal ganglia. Filariae may die after having invaded the soft tissues, then they become calcified, to show up on roentgenograms as small linear or dotlike shadows, 1 to 4 mm. long, and 1 mm. wide, in the subcutaneous tissues, lymph nodes and scrotal lymphatics. Garland stated that they are difficult to recognize at times, but are fairly characteristic, having a distribution in the body different from calcified trichinae, and much smaller than cysticerci. Cysticerci are the larval forms of *Tænia solium*, the pork tapeworm. They may invade any organ in the body. Calcification of the larvæ occurs but rarely before 5 years after infection. It is seen most frequently in the skeletal muscles, less often in the brain. In the muscles the calcified masses are elongated and lie in the direction of the muscle fibers. They vary greatly in size, shape, and number. In the brain the masses are smaller and tend to be scattered in the substance of the organ. Calcified trichinae also appear in the skeletal muscles; they are small, compared with cysticerci, and do not tend to be elongated. Larger elongated, coiled and segmented shadows of calcification in the soft tissues of the leg and trunk have been described in dracontiasis, caused by the guinea worm, *Dracunculus medinensis*, a parasite formerly classified as *Filaria medinensis*. Garland stated that the large size of these calcified worms renders them readily recognizable, their favorite location being in the subcutaneous tissues of

the leg. Calcification in the submucous tissues of the large intestine and urinary tracts has been observed in schistosomiasis, caused by *Schistosoma* or blood flukes. The disease is also known as bilharziasis. The flukes enter the body through an abrasion of the skin. Garland stated that any organ of the body may be invaded, but the intestinal and urinary tracts are involved most frequently and most severely. Bleeding from one or both of these tracts is the most common symptom. The diagnosis is made by finding the ova in the excreta. The ova that have been deposited in the submucosal structures cause ulceration, necrosis, and ultimately calcification. This calcification appears on roentgenograms in streaklike form in the wall of the viscera affected or in ovoid masses which have the appearance of calculi or calcified papillomas.

The principal tropical disease manifested by roentgenologically demonstrable lesions of the lungs are: (1) distomiasis, caused by the trematode *Paragonimus westermani*; (2) echinococcosis, caused by the larval form of the dog tapeworm; (3) Q fever, caused by *Rickettsia diaporica* or *burneti*. Garland made brief descriptions of the roentgenologic changes produced in the lungs in all of these diseases. None of them are very characteristic, except the hydatid cysts of echinococcal origin.

Lesions of bones are seen in a number of tropical diseases. In echinococcosis irregular cystic lesions develop, especially in the ribs and pelvic bones, which resemble fibrocystic disease of bone or osteolytic metastatic carcinoma. Osseous lesions, similar to those seen in syphilis, develop in the diseases caused by various

forms of *Treponema*. Yaws, pinta, and bejel are examples. Goundou, a chronic sclerosing osteoperiostitis of the superior maxillæ, and gangosa, a destructive ulcerating disease of the nose and palate, are tertiary forms of yaws, caused by *Treponema pertenue*. The diseases respond favorably to antisiphilic treatment. Lesions of bone, more or less typical, are also encountered in leprosy, Madura foot, ainhum and in various types of tropical ulcers caused by spirochetal and bacillary organisms.

Roentgen therapy has been used with favorable results in the treatment of the lymphangitis, lymphadenitis and chyluria of filariasis. It also was used successfully in the treatment of acne vulgaris and epidermophytosis, diseases which are not tropical, but which tend to undergo severe exacerbation under some tropical conditions.

Very briefly stated, these are the principal considerations that seem thus far to have developed from recently gained experience with roentgenologic manifestations of tropical diseases. Instances will probably be infrequent when the roentgenologic findings will yield the final diagnosis. Roentgenologists and their consultants in internal medicine should be prepared, however, to think in terms of tropical diseases and their late sequelæ. Physicians who have had experience in tropical areas with our armed forces probably have become accustomed to keeping these possibilities in mind. Those who have not had such opportunities will add this group of diseases to those with which they have, until now, been more familiar.

REFERENCES

- (1.) Buie, L. A.: Practical Proctology, Phila., Saunders, 512 pp., 1937.
- (2.) Clark, H. C.: Quoted by Golden, R., and Ducharme, P.
- (3.) Craig, C. F.: Quoted by Golden, R., and Ducharme, P.
- (4.) Druckmann, A., and Schorr, S.: Am. J. Roentgenol., 54, 145, 1945.
- (5.) Faust, E. C.: Quoted by Golden, R., and Ducharme, P.
- (6.) Garland, L. H.: Radiology, 44, 1, 1945.
- (7.) Golden, R.: Radiologic Examination of the Small Intestine, Phila., Lippincott, 239 pp., 1945.
- (8.) Golden, R., and Ducharme, P.: Radiology, 45, 565, 1945.
- (9.) Hodes, P. J., and Keefer, G. P.: Am. J. Roentgenol., 54, 728, 1945.
- (10.) Krause, G. R., and Crilly, J. A.: Am. J. Roentgenol., 49, 719, 1943.
- (11.) Weber, H. M.: Am. J. Roentgenol., 30, 488, 1933.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 19, 1946

OWING to the meetings of the Federation of American Societies for Experimental Biology at Atlantic City in March, the March session of the Physiological Society of Philadelphia was not held.

BOOK REVIEWS AND NOTICES

RECENT ADVANCES IN NEUROLOGY AND NEUROPSYCHIATRY. By W. RUSSELL BRAIN and E. B. STRAUSS. Fifth ed. Pp. 363; 32 illus. Philadelphia: Blakiston, 1945. Price, \$5.00.

THE latest edition of this "ancillary text-book of neuropsychiatry" is a welcome revision of a book whose usefulness is demonstrated by the fact that this is a 5th edition. It is written with a clarity apparent in other works by the same author. It is particularly useful since it reviews literature not always generally available during the war years.

Of particular interest are the studies of conditions seen in connection with war wounds, especially injuries of the brain and of the peripheral nerves; recent studies of vestibular functions and Ménière's syndrome, especially in this connection the re-interpretation of caloric vestibular tests. An interesting section discusses the demyelinating diseases of the nervous system, and a summary of neurotropic virus diseases also appears here. In keeping with its extended use is a section on electroencephalography.

The general contents are more concerned with the neurologic aspects of neuropsychiatry than the psychiatric. This point of view is illustrated in the sentence discussing the difference between Pick's disease and Alzheimer's disease, "to put it pithily, one might say that if one performed prefrontal leucotomy on a case of Alzheimer's disease one would produce the clinical picture of Pick's disease."

The book can be recommended highly.

G. G.

SYNOPSIS OF GYNECOLOGY. By H. S. CROSSEN, M.D., F.A.C.S., and R. J. CROSSEN, M.D., F.A.C.S. St. Louis: Mosby, 1946: Price, \$3.00.

THIS 3rd edition of Crossens' "Synopsis of Gynecology" is like its predecessors, intended principally for "medical students who intend to follow distant branches of their profession" and for practicing physicians as a "compact presentation of the outstanding features" of gynecology.

The publishers have compressed a good short text-book into 233 pages by clever use of space and by marked reduction in the size of the print. The latter feature, however, renders prolonged reading rather difficult. The chapters, with their subdivisions, are clearly titled and the index is accurate and ample.

The subject matter is presented in a concise and readable manner and very few deletions are made for the sake of brevity. The book contains 135 accurate, clear illustrations, many of which are diagrammatic. The chapters upon genital anatomy and physiology and upon menstrual disturbances are up-to-date and clearly written. The section upon genital embryology and malformations is exceptionally lucid and practical. The discussion of ovarian tumors is inadequate, however, as the solid tumors of the ovary receive only scant mention.

As is true of most text-books upon a living subject, the lapse of time between the editing and the publishing has permitted the appearance of new subject material that could not be included. The book contains a minimum of information concerning chemotherapy in

gynecology and no information concerning the antibiotic agents or the Rh blood factor.

It is doubtful that the "Synopsis" will be acceptable as a text-book for medical students whose ideas have not been crystallized concerning specialization at such an early age. On the other hand, it is admirably adapted for the purpose of a rapid review or a hurried reference by students, house officers, and busy practicing physicians. F. P.

NEW BOOKS

Asclepius. Book I. By EMMA J. EDELSTEIN and LUDWIG EDELSTEIN. Pp. 479. Baltimore: Johns Hopkins Press, 1945. Price, \$7.50.

Asclepius. Book II. By EMMA J. EDELSTEIN and LUDWIG EDELSTEIN. Pp. 277. Baltimore: Johns Hopkins Press, 1945. Price, \$7.50.

Hippocratic Wisdom. By WILLIAM F. PETERSEN, M.D. A Modern Appreciation of Ancient Scientific Achievement. Pp. 263. Springfield: Thomas, 1946. Price, \$5.00.

Minerva's Progress. By ALFRED E. COHN. Pp. 101. New York: Harcourt, Brace, 1946. Price, \$2.00.

An Introduction to Essential Hypertension. By RICHARD F. HERNDON, M.D., F.A.C.P. Pp. 88. Springfield: Thomas, 1946. Price, \$2.50.

Group Psychotherapy (Theory and Practice). By J. W. KLAPMAN, M.D., Faculty, Northwestern Univ. Med. School; Member, Board of Psychiatry and Neurology; Staff of the Inst. of Juvenile Research. Pp. 320. New York, Grune & Stratton, 1946. Price, \$4.00.

The Chemistry of Anesthesia. By JOHN ADRIANI, M.D., Director, Dept. of Anesthesia, Charity Hosp. of Louisiana at New Orleans; Clinical Assist. Prof. of Surgery, Louisiana State Univ. School of Med. Pp. 536. Springfield: Thomas, 1946. Price, \$7.00.

The Extremities. By DANIEL P. QUIRING, Ph.D., Head of the Anatomy Div., Cleveland Clinic Foundation and Assoc. Prof. of Biology, Western Reserve Univ.; BEATRICE BOYLE, Artist, Cleveland Clinic Foundation; ERNA L. BOROUSH, M.A., Anatomy Research Div., Cleveland Clinic Foundation. Pp. 117; 107 illus. Philadelphia: Lea & Febiger, 1945. Price, \$2.75.

Preventive Medicine and Public Health. By WILSON G. SMILLIE, A.B., M.D., D.P.H., Sc.D. (HON.), Professor of Public Health and Preventive Medicine, Cornell Univ. Med. Coll., New York. Pp. 607. New York: Macmillan, 1946. Price, \$6.00.

Medicine in Industry. By BERNHARD J. STERN, Ph.D., Lecturer in Sociology, Columbia Univ.; Visiting Prof. of Sociology, Yale Univ. Pp. 209. New York: Commonwealth Fund, 1946. Price, \$1.50.

Nutrition and Chemical Growth in Childhood. Vol. II. Original Data. By ICIE G. MACY, Ph.D., Sc.D., Director of Research Laboratory, Children's Fund of Michigan; Past-Pres., American Inst. of Nutrition; Member of Food and Nutrition Board of the National Research Council; Consultant for Nutrition to the Pediatric Staff of the Children's Hospital of Michigan; Hon. Member of the Society for Pediatric Research; Member of the American Society of Biological Chemists and the Society for Research in Child Development. Pp. 1460, including Index to Vols. I and II. Springfield: Thomas, 1946. Price, \$10.00.

Ambulatory Proctology. By ALFRED J. CANTOR, M.D., Associate Proctologist, Kew Gardens Gen. Hosp., Long Island, N. Y.; formerly Assist. Attending Gastro-enterologist, Queens Gen. Hosp.; Assist. Adj. Proctologist, Hosp. for Joint Diseases, New York. With a Foreword by BEAUMONT S. CORNELL, M.D., Editor, Am. J. Digest. Dis. Pp. 524; 281 illus. New York: Hoeber, 1946. Price, \$8.00.

Exercises in Human Physiology (Preparatory to Clinical Work). By SIR THOMAS LEWIS, C.B.E., F.R.S., M.D., D.S.C., LL.D., F.R.C.P., Physician-in-Charge of Dept. of Clinical Research, Univ. Coll. Hosp., London; Hon. Consulting Physician to the Ministry of Pensions; Consulting Physician, City of London Hosp.; Fellow of Univ. Coll., London. Pp. 103; 8 illus. London: MacMillan, 1945. Price, \$1.25.

Western Reserve University Centennial History of the School of Medicine. By FREDERICK CLAYTON WAITE, Prof. Emeritus in Western Reserve Univ. Pp. 588; 16 illus. Cleveland: Western Reserve Univ. Press, 1946. Price, \$6.00.

Physical Chemistry for Premedical Students. By JOHN PAGE AMSDEN, Prof. of Chemistry, Dartmouth Coll. Pp. 208. New York: McGraw-Hill, 1946. Price, \$3.50.

A Textbook of Bacteriology and Immunology. By JOSEPH M. DOUGHERTY, A.M., M.A., Ph.D., Dean of the School of Science and Prof. of Bacteriology, Villanova Coll.; Fellow of the American Association for the Advancement of Science; and ANTHONY J. LAMBERTI, B.S., M.S., Instructor in Bacteriology and Parasitology, Temple Univ. School of Med.; formerly Instructor in Bacteriology, Villanova Coll.; Member of the American Public Health Association. Pp. 360; 102 illus. St. Louis: Mosby, 1946. Price, \$4.50.

Colloid Chemistry, Theoretical and Applied. Vol. VI, General Principles and Specific Industries, Synthetic Polymers and Plastics. By Selected International Contributors. Collected and edited by JEROME ALEXANDER. Pp. 1215. New York: Reinhold Publ. Corp., 1946. Price, \$20.00.

Bioenergetics and Growth. With Special Reference to the Efficiency Complex in Domestic Animals. By SAMUEL BRODY, Ph.D., Chairman, Committee on Growth and Energy Metabolism, Coll. of Agriculture, Univ. of Missouri, Columbia, Mo. Publication of the Herman Frasch Foundation. Pp. 1023. New York: Reinhold, 1945. Price, \$8.50.

Principles of Dynamic Psychiatry. By JULES H. MASSERMAN, M.D., Division of Psychiatry, Dept. of Medicine, Univ. of Chicago. Pp. 322; 4 illus. Philadelphia: Saunders, 1946. Price, \$4.00.

Oral Medicine. By LESTER W. BURKET, M.D., D.D.S., Prof. of Oral Medicine, The Thomas W. Evans Museum and Dental Inst. School of Dentistry, Univ. of Penna.; Prof. of Oral Medicine, Graduate School of Medicine. Pp. 674; 350 illus. Philadelphia: Lippincott, 1946. Price, \$12.00.

Modern Management in Clinical Medicine. By F. KENNETH ALBRECHT, M.D., S.A. Surgeon, U. S. Public Health Service; Kansas State Tuberculosis Consultant; formerly Clinical Director, U. S. Marine Hosp., Baltimore, M. D. Pp. 1238; 237 illus. Baltimore: Williams & Wilkins, 1946. Price, \$10.00.

Nursing and Nursing Education. By AGNES GELINAS, R.N., A.M., Professor of Nursing and Chairman of the Skidmore Coll. Dept. of Nursing, New York Post-Graduate Medical School and Hosp. Pp. 84. New York: Commonwealth Fund, 1946. Price, \$1.00.

Nursing in Commerce and Industry. By BETHEL J. McGRATH, R.N. For the National Organization for Public Health Nursing. Pp. 372. New York: Commonwealth Fund, 1946. Price, \$3.00.

The Sulphonamides in Theory and Practice. By J. STEWART LAWRENCE, M.D., M.R.-C.P., Physician, Haymeads Emergency Hosp., Bishop's Stortford, England. Pp. 125. London, Lewis, 1946. Price, 9s (\$1.80).

New Drugs. By ARTHUR D. HERRICK, author of "Drug Products; Labeling, Packaging, Regulation" and "Food Regulation and Compliance." With FOREWORD by AUSTIN E. SMITH, M.D., Secretary, Council on Pharmacy and Chemistry of the American Medical Assn. Pp. 319. New York: Revere. Price, \$4.00.

Roentgen Diagnosis of Diseases of the Gastro-intestinal Tract. By JOHN T. FARRELL, JR., M.D., Clinical Prof. of Radiology, Graduate School of Medicine, Univ. of Penna.; Radiologist, Hermann Hessenbruch Memorial Dept. of Radiology, The Lankenau Hosp., Children's Hosp. of the Mary J. Drexel Home and White Haven Sanatorium; Consulting Roentgenologist, Frederick Douglass Memorial Hosp., and Mercy Hosp. Pp. 271; 190 illus. Springfield: Thomas, 1946. Price, \$5.50.

NEW EDITIONS

Clinical Electrocardiography. By DAVID SCHERF, M.D., F.A.C.P., Associate Prof. of Medicine, New York Medical Coll., Flower and Fifth Ave. Hosps.; and LINN J. BOYD, M.D., F.A.C.P., Prof. of Medicine, New York Medical Coll., Flower and Fifth Ave. Hosps. Second ed. Pp. 267; 409 illus. Philadelphia: Lippincott, 1946. Price, \$8.00.

Kettle's Pathology of Tumors. By W. G. BARNARD, F.R.C.P., Prof. of Pathology, Univ. of London, at St. Thomas' Hosp. Med. School; Director of Pathology, St. Thomas' Hosp., London; and A. H. T. ROBB-SMITH, M.A. (OXON.), M.D. (LOND.), Nuffield Reader in Pathology, Univ. of Oxford; Director of Pathology, Radcliffe Infirmary. Third ed. Pp. 318; 191 illus. New York: Hoeber, 1946. Price, \$5.50.

The Electron Microscope. By E. F. BURTON, Head of the Dept. of Physics and Director of the McLennan Laboratory, Univ. of Toronto, Canada; and W. H. KOHL, formerly Chief Engineer, Rogers Electronic Tubes, Ltd., Toronto, Canada. Second ed. Pp. 325. New York: Reinhold, 1946. Price, \$4.00.

Hospital Care of the Surgical Patient. A Surgeon's Handbook with an appendix on The Treatment of Wounds. By GEORGE CRILE, JR., M.D., Surgeon, Cleveland Clinic; and FRANKLIN L. SHIVELY, JR., M.D., Assist. Surgeon, Cleveland Clinic. With a Foreword by EVARTS A. GRAHAM, M.D., Bixby Professor of Surgery, Washington Univ. School of Medicine, St. Louis. Second ed. Pp. 288. Springfield: Thomas, 1946. Price, \$3.50.

The Diagnosis of Nervous Diseases. By SIR JAMES PURVES-STEWART, K.C.M.G., C.B., Knight of St. John of Jerusalem, M.D. (EDIN.), F.R.C.P., Consulting Physician to Westminster Hosp., West End Hosp. for Nervous Diseases, and Royal National Orthopedic Hosp.; Membre Correspondant de la Société de Neurologie de Paris; Honorary Member of the American Neurological Association and of the Neurological Societies of Philadelphia, New York, Copenhagen, Estonia, Buenos Aires, and Chile. Ninth ed. Pp. 880; 358 illus. Baltimore: Williams & Wilkins, 1945. Price, \$11.00.

Skin Diseases in Children. By GEORGE M. MACKEE, M.D., Prof. of Clinical Dermatology and Syphilology, New York Post-Graduate Medical School, Columbia Univ., New York; and ANTHONY C. CIPOLLARO, M.D., Associate in Dermatology and Syphilology, New York Post-Graduate Medical School, Columbia Univ., New York. Second ed. Pp. 448; 225 illus. New York: Hoeber, 1946. Price, \$7.50.

Irish Medical Directory and Hospital Year Book 1945. Eighth ed. Pp. 296. Dublin: Parkside Press, 1945.

The Physiological Basis of Medical Practice. By CHARLES H. BEST, C.B.E., M.A., D.Sc. (LOND.), F.R.S., F.R.C.P. (CAN.), Prof. and Head of Dept. of Physiology, Director of Banting-Best Dept. of Medical Research, Univ. of Toronto; and NORMAN BURKE TAYLOR, V.D., M.D., F.R.S. (CAN.), F.R.C.S. (EDIN.), F.R.C.P. (CAN.), M.R.C.S. (ENG.), L.R.C.P. (LOND.), Prof. of Physiology, Univ. of Toronto, Canada. Fourth ed. Pp. 1169. Baltimore: Williams & Wilkins, 1945. Price, \$10.00.

Protozoölogy. By RICHARD R. KUDO, D.Sc., Prof. of Zoölogy, Univ. of Illinois. Third ed. Pp. 778; 336 illus. Springfield: Thomas, 1946. Price, \$8.00.

Howell's Textbook of Physiology. By JOHN F. FULTON, M.D., Sterling Prof. of Physiology, Yale Univ. School of Medicine. Fifteenth ed. Pp. 1304. Philadelphia: Saunders, 1946. Price, \$8.00.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JUNE, 1946

ORIGINAL ARTICLES

HEREDITARY (?SEX-LINKED) ANEMIA*

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THE hereditary nature of numerous hematologic disorders, hemophilia, hereditary hemorrhagic telangiectasia, etc., is well established and generally recognized. Among the inherited blood diseases there are 3 well-defined and not uncommon types of anemia, namely, the anemia associated with familial hemolytic icterus, sickle cell anemia, and Mediterranean anemia. These anemias, in addition to their hereditary factor of etiology, have several features in common. Striking abnormalities in the structure and physiologic behavior of the red blood cells occur in all of them, as well as a tendency toward chronic and sometimes acute episodes of red blood cell hemolysis. Sickle cell anemia, with its underlying erythrocyte abnormality, the sickle cell trait, and Mediterranean anemia are almost exclusively confined by accident or otherwise to certain racial groups. The Mediterranean disease occurs in a mild asymptomatic form as well as in a severe and ordinarily fatal form, Cooley's anemia.^{1,8,11,19,23,28,32,34,35,41,42,44} It differs perhaps fundamentally from the other hereditary anemias in that a grave defi-

ciency of hemoglobin in the circulating red blood cells occurs, possibly due to an inborn abnormality of pigment metabolism.⁴³ The erythrocytes show great variation in size and in shape; nucleated red cells are seen in those with severe anemia; some individuals have predominantly oval or elliptical cells and others have many "target" cells.^{2,8,11,37,42} It is important to differentiate here another type of inherited erythrocyte anomaly which is usually of no clinical significance. Elliptocytosis, or ovalocytosis, is known to occur in non-Mediterranean families without either anemia or other evidence of disease being present.^{3,14,26,45}

Aside from the 3 well-known varieties of inherited anemia, it is not too uncommon in hematologic practice to encounter patients with an anemia associated with unusual degrees of red blood cell malformation, sometimes with icterus and splenomegaly, whose disease appears to be atypical or of uncertain origin. Many isolated case reports of this type have been published.^{5,9,13,15,16,18,24,25,30,31,33,39,42} The hereditary nature of such conditions may easily be overlooked, and confirmatory

* Part of the expense of this research was met by the Horace H. Rackham School of Graduate Studies.
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studies are not always possible. In any case it is rare for the family group to be large enough to permit a satisfactory investigation of the hereditary and genetic aspects.

We have had under our observation recently 2 families of non-Mediterranean origin in whom there has recurred through several generations a distinctive type of hypochromic anemia associated with abnormal red blood cells and enlargement of the spleen. Our attention was drawn to the first family by the diagnostic problem presented by a 32 year old soldier who had just been discharged from the army because of a severe anemia of unknown etiology. The character of his blood findings and the fact that his maternal grandfather was known to have had an enlarged spleen all his life with symptoms suggestive of a chronic anemia led us to suspect that a familial type of blood dyscrasia was present. When we discovered that his mother had an enlarged spleen even though her blood values were normal, a complete family investigation appeared desirable. Medical histories, physical examinations and blood studies on all the available relatives, 29 in all, were obtained, largely by field trips to their homes. A severe anemia with splenomegaly was discovered in a brother who had previously been considered perfectly well. In addition to his mother, 4 other female relatives were found to have enlarged spleens or minor blood abnormalities.

In the second family at least 16 males scattered through 5 generations had died of severe anemia during infancy or adolescence. Two brothers afflicted with the anemia were living. One boy's health was precarious and the other required blood transfusions at regular intervals to keep him alive. An investigation similar to that carried out in the first family was accomplished with 18 members being available for study. No unsuspected cases of anemia were found, but 6 of the female relatives, including the afflicted boy's mother and grandmother, were

shown to have red blood cell abnormalities and in some cases splenomegaly.

Procedure. To study in some detail the genetic linkage underlying the blood abnormalities in these families, a number of tests and measurements were made in order that the occurrence of traits having an established inheritance pattern might be compared with the hematologic findings. The bloods were typed with respect to the agglutinogens A₁, A₂, B, M, and N. Determination of the taste reaction to phenylthiocarbamide, tests of color vision and eye dominance, and tests of handedness were made. The "secretor factor" was determined on the saliva by means of human A and B serums. The results of these tests and their genetic significance will be discussed separately.

The pedigree charts (Figs. 1 and 3) differ from the conventional diagram by having the children of a single union arranged in a vertical column in the order of their birth rather than horizontally. The sibships are numbered 1 to 18 in Family I, and 1 to 19 in Family II. A specific individual will be referred to by means of the sibship number followed by a number denoting his or her position from top to bottom, corresponding to birth order, within the sibship. Thus, 11-1 of Family I refers to the anemic male first studied, whose grandfather, 2-3, appeared to be the first member of the family to have the disease.

The hematologic findings are given in Tables 1 and 2. Only the data pertaining to the afflicted individuals, their parents, siblings, and those relatives with splenomegaly or minor blood abnormalities are given.

Platelet counts unless otherwise specified were in all cases normal. Prothrombin determinations were done in a few cases, but being normal were deleted along with other various negative findings. It was not possible to get adequate Rh typing at the time.

FAMILY I (Heredity Clinic No. 606). This family was of German, Scotch and English origin, without any of the living members or known ancestors being of Mediterranean stock. The family pedigree is given in Figure 1. Generations I through III originated in Wisconsin and followed farming and laboring occupations. There were no mental abnormalities nor physical stigmata

known in the family. The first member of the family who appeared to be affected with the anemia (2-3) was the grand-father of our first patient. He was always pale, never able at any time during his adult life to do more than light work, and he suffered from numerous fainting spells. A large spleen was said to have been present for

histories of the remaining members of this family and their descendants follow.

R. F. (6-1) was 57 years of age. Except for a period of gastro-intestinal symptoms thought to be due to peptic ulceration he had always been well. A physical examination and a complete blood examination (Table 1) revealed no abnormalities. One

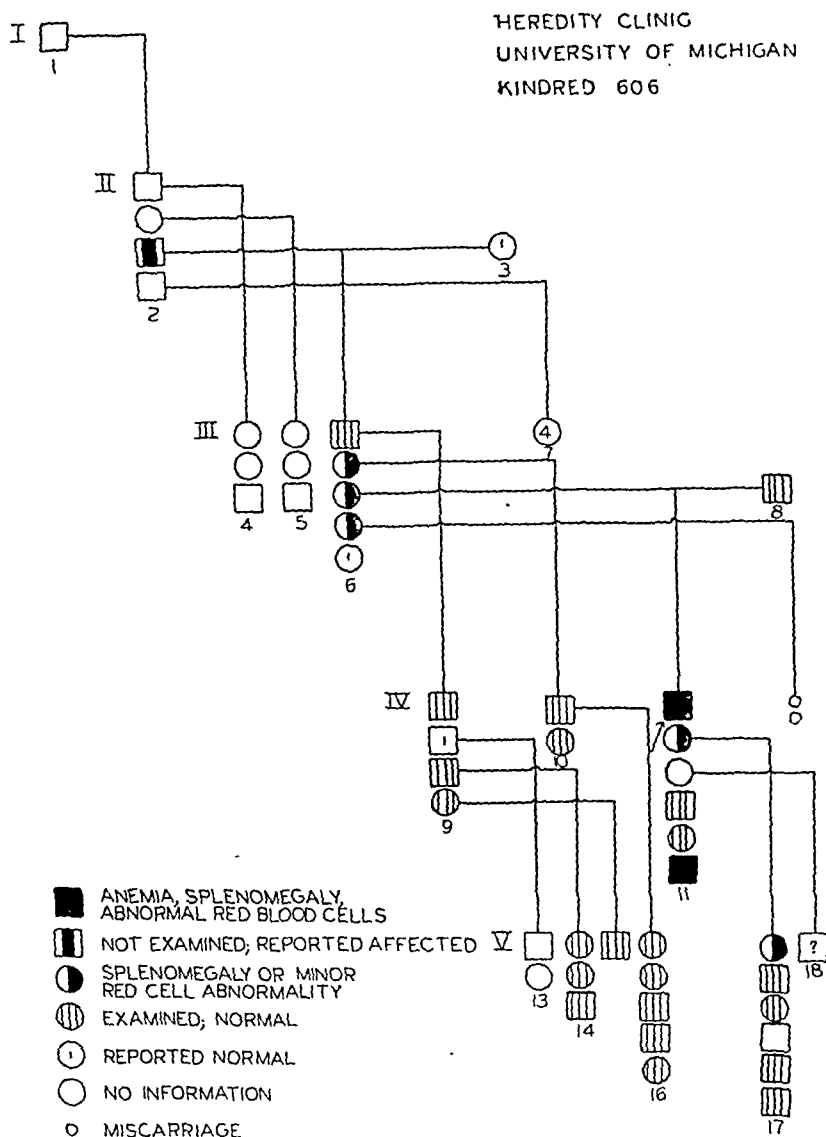


FIG. 1.—Pedigree chart of Family I. Males are indicated by squares, females by circles.

many years but no blood examinations were ever made. He lived to be 62 years of age. There were 5 children in his family and 4 of them were living and available for examination. His youngest daughter (6-5) died of an infectious disease when 11 to 12 years old. She was thought not to be anemic nor to have had an enlarged spleen. The case

of his sons was serving in the army and was not available for examination. The 3 remaining children and 4 grandchildren were healthy, and complete blood and physical examinations revealed no abnormalities.

L. M. F. (6-2) was a 55 year old housewife. She had had no unusual illnesses, no symptoms of anemia, nor jaundice. A

TABLE I.—SUMMARY OF BLOOD FINDINGS IN FAMILY I

Identity	Age, sex	Hb. (gm. per 100 cc.)	RBC (mill. per c.mm.)	Hemato-crit	M.C.V. (cu.)	M.C.H. (μg.)	M.C.H.C. (%)	Morphology of RBC	Reticulo-cyte (%)	Range of hemolysis in hypotonic NaCl solutions	Blood type	Other findings
R. F. 6-1	57 M	16.9	5.4	46.5	86	31.3	36.4	Normal	OMN	
L. M. F. 6-2	55 F	14.2	4.9	40.5	83	29.0	35.0	Anisocytosis +, oval cells 6%				
R. F. P. 6-3	51 F	15.1	4.9	44.5	91	30.8	34.0	Anisocytosis +, oval cells 6%	0.5	0.60-0.45 0.55-0.40*	A ₁ MN	Splenomegaly
J. P. 8-1	55 M	16.5	5.7	48.0	84	29.0	34.4	Normal	..	0.50-0.35 0.55-0.45*	A ₁ MN	
B. F. B. 6-4	44 F	12.4	4.2	38.5	92	29.5	32.2	Anisocytosis +, oval cells 5%	0.4	...	A ₁ BMN	
G. P. 11-1	32 M	9.1	6.4	35.0	55	14.2	26.0	Anisocytosis + + + +, poikilocytosis + + + +, target cells 6%	3.1	0.55-0.15 0.55-0.35*	A ₁ M	Splenomegaly, hepatomegaly
L. P. C. 11-2	30 F	15.4	5.0	45.0	90	30.8	34.2	Anisocytosis +	2.0	0.55-0.40 0.55-0.35*	A ₁ M	
H. P. 11-5	23 F	15.0	4.6	42.3	92	32.6	35.5	Normal	..	0.50-0.40 0.55-0.40*	A ₁ N	
R. P. 11-6	15 M	10.4	5.5	35.7	65	18.9	29.1	Anisocytosis + + + +, poikilocytosis + + + +, target cells 0.5%	1.0	0.50-0.25 0.55-0.45*	A ₁ MN	Splenomegaly
L. C. 17-1	10 F	13.1	4.9	Anisocytosis +	0.5	...	A ₁ MN	Splenomegaly
R. M. 18-1	3½ M	15.5	5.4	Anisocytosis +, poikilocytosis +, spherocytes 10%	OMN	Palpable liver and spleen

* Normal control.

physical examination showed no abnormalities. The blood examination showed that there was no anemia but in the stained films the red blood cells varied beyond normal in size and 6% were oval in shape. Her 2 children and 5 grandchildren were likewise examined and found to be normal.

B. F. B. (6-4). This 44 year old married woman had had good general health. When 31 years old she had a prolonged febrile illness thought to be due to a brucella infection. Two miscarriages in mid-pregnancy occurred some years later. When 41 years of age symptoms of a severe anemia led to the discovery of a hemoglobin level 43% of normal. This was attributed to hypermenorrhea associated with uterine fibroids, and the blood counts improved with treatment. Physical examination showed no abnormalities and the peripheral blood values were within range of normal (Table 1). The red blood cells varied somewhat beyond the usual in size, 5% of them were oval in shape, but all were well and uniformly filled with hemoglobin.

R. F. P. (6-3). This 51 year old woman, the mother of 2 anemic sons, had always had good general health. She had never been anemic or jaundiced and splenomegaly had never been previously discovered. A physical examination showed that she was well developed and well nourished. No physical abnormality was found other than an enlarged, firm, movable spleen, the tip of which descended 3 to 4 cm. below the costal margin with inspiration. The peripheral blood values and red cell fragility tests were normal (Table 1). The red blood cells varied slightly beyond normal in size and a small percentage of them were oval shaped but well and uniformly filled with hemoglobin. Her husband (J. P., 8-1) had had no illnesses other than asthma which was associated with exposure to dusts. There was no consanguinity. A physical examination revealed no relevant abnormalities and his blood values and red cell fragility tests were normal.

G. P., No. 542654 (11-1). This 32 year old son of R. F. P. (6-3) was admitted to the Simpson Memorial Institute on Feb. 28, 1944, shortly after being discharged from the United States Army. His general health had been perfectly good until 2½ years earlier when an acute febrile illness led to his admission to a local hospital. An en-

larged spleen was discovered and it was thought that he had malaria. The fever subsided after a few days and the spleen became smaller. He soon felt well again and returned to his work in an automobile factory.

In June 1943, he was inducted into the Army. He was able to perform all the training exercises except that he was unable to march double time for more than 1 or 2 blocks. In the latter part of November 1943, he developed a mild upper respiratory infection and while on a hike became weak and short of breath. At the station hospital that evening a temperature of 103° F. was found. The fever continued for several days. He was told that he was jaundiced, that his liver and spleen were enlarged, and that his hemoglobin was 40% of normal. Coincident with the administration of iron he gradually improved and was discharged from service 10 weeks later. He consulted us because his final discharge diagnosis appeared to be uncertain and the outlook was worrisome.

Physical examination on admission to the hospital showed the patient to be well developed and well nourished. His complexion was yellowish but there was no visible icterus. The blood pressure was normal. Examination of the head and neck revealed no abnormalities. The heart and lungs were normal. The liver was enlarged, the lower edge extending across the abdomen 10 cm. below the ensiform process to a point 5 cm. below the lateral rib margins on the right side. The spleen was enlarged to fill the left upper quadrant of the abdomen, the tip being palpable 5 cm. below the costal margin at respiratory rest. The remainder of the physical examination showed nothing abnormal.

A urinalysis, Kahn test, and a stool examination were negative. The serum bilirubin was 0.83 mg. per 100 cc. and the urine urobilinogen excretion was slightly increased. Roentgen examination of the upper gastro-intestinal tract showed no intrinsic abnormality but confirmed the finding of an enlarged liver and spleen. The gall bladder was not made visible. Roentgenograms of the chest, hands, wrists, and skull were not abnormal. The cephalin flocculation test and bromsulphthalein test showed no evidence of impaired liver function. Examination of the peripheral blood

disclosed a severe hypochromic microcytic anemia (Table 1). The red blood cells showed extreme variation in size, in shape and in hemoglobin content (Fig. 2, A). In fresh sealed preparation the bizarre red cell forms were equally conspicuous and after 48 and 72 hours there was no change in morphology. No nucleated red blood cells were present. The erythrocytes showed some increased resistance to hemolysis in hypotonic sodium chloride solutions. The white blood cell and differential counts were normal, and there was no shift toward immaturity in the myeloid cells.

The bone marrow obtained by sternal puncture was less cellular than normal. The predominant nucleated cells were relatively mature granulocytes with a small

had enjoyed good health except for biliary colic and jaundice due to cholelithiasis for which a cholecystectomy had been done. Physical examination showed pronounced obesity. The liver was palpable 2 to 3 cm. below the right costal margin but the spleen could not be felt. The peripheral blood values were within the average range for healthy individuals. The red blood cells varied beyond normal in size and a few were oval in shape and somewhat deficient in hemoglobin content.

Five of her 6 children were living, in good health, and available for examination. Her fourth child, a boy, had died at 9½ months, of congenital heart disease. L. C. (17-1), the oldest girl, enjoyed robust health and had never been anemic, jaundiced, nor had

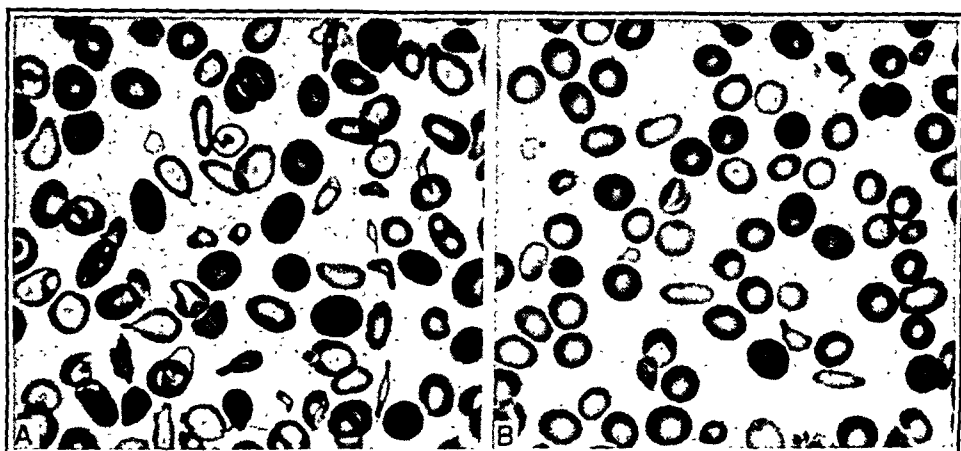


FIG. 2.—Stained blood films of the anemic males in Family I. A, G. P., 11-1; B, R. P., 11-6.

percentage of myelocytes. Typical hemohistiocytes were present. Normoblasts were fairly numerous, erythroblasts less common, and megaloblasts rare and atypical. The myeloid-erythroid ratio was about 5 to 1. A splenic puncture was done and the spread films contained clumps of mononuclear phagocytic cells. There was no evidence of splenic hematopoiesis.

The patient was afebrile and entirely comfortable during his hospital stay and after discharge he was able to resume heavy labor. There was no change in the blood values after several weeks of iron therapy. Nine months later his general condition remained unchanged and his blood values were unaltered.

L. P. C. (11-2), the 30 year old sister of G. P. (11-1) and the mother of 6 children,

chills or fever. Physical examination on 2 occasions several months apart showed as the only abnormality an enlarged spleen, the broad, rounded tip of which descended 2 to 3 cm. below the costal margin with inspiration. Her blood values (Table 1) were not abnormal. A few of the RBC were oval in shape, but well and uniformly filled with hemoglobin. In fresh, moist preparations there was no sickling after 48 hours. Similar physical and blood examinations in the 4 younger children in this family showed no abnormalities.

E. P. (11-3) had always been considered perfectly healthy but died at the age of 23 years of a postpartum pulmonary embolus. Her 3½ year old son (18-1) had been unusually susceptible to childhood diseases and during infancy he had had rickets. He

had had no known anemia and had never been jaundiced. Physical examination on 2 occasions, several months apart, showed both the liver and spleen to be palpable 1 to 2 cm. below their respective costal margins. The red blood cell count and hemoglobin values were normal. The red blood cells were mostly round but they varied

beyond normal in size and in shape, and about 10% of the cells were spherocytes.

H. P. (11-4) was considered healthy in all respects and was in active service in the Army. Blood counts forwarded from the Far East by Major Charles A. Armbrust were normal.

H. P. (11-5) was a 23 year old factory

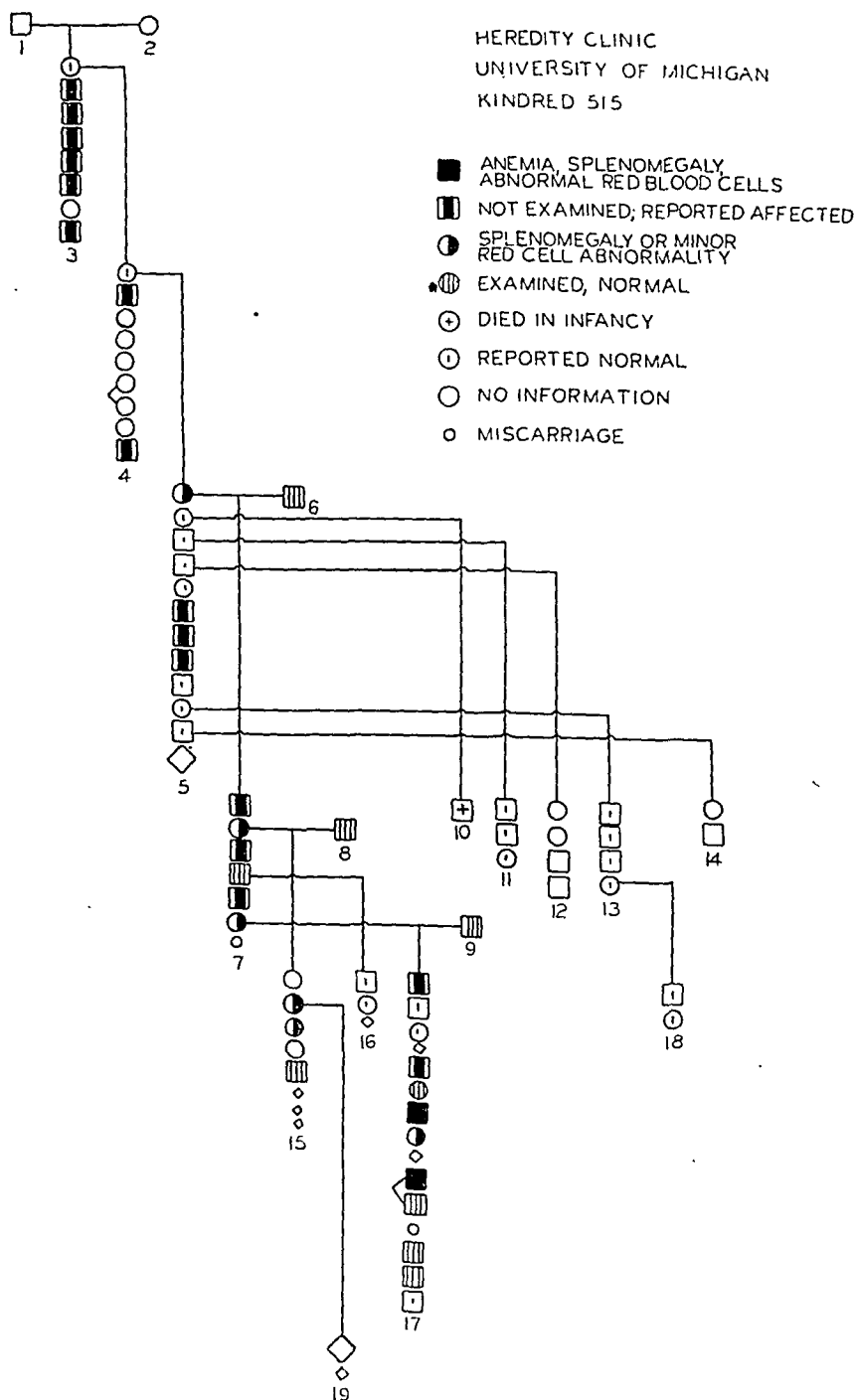


FIG. 3.—Pedigree chart of Family II.

worker. She had been jaundiced for a few weeks 4 years previously. On physical examination a tender liver edge was palpable just below the costal margin, but the spleen was not palpable. Blood counts and fragility tests were normal and the red blood cells were normal in morphology.

R. P. (11-6), the youngest brother of G. P. (11-1), was a 15 year old schoolboy who had always enjoyed robust health. He was fond of strenuous sports and had never been jaundiced nor had unusual febrile episodes. A complete physical examination showed no abnormality other than an enlarged spleen the lower border of which was palpable 2 to 3 cm. or more below the left costal margin.

Examination of the peripheral blood on different occasions showed a hypochromic microcytic anemia slightly less severe than of his brother (Table 1). The red blood cells varied greatly in size, shape and hemoglobin content (Fig. 2, B), and there was increased resistance to hemolysis in hypotonic salt solutions. The white blood cells and differential counts were normal.

FAMILY II (Heredity Clinic No. 515). This family originated from English, Dutch and Swiss stock which was without known Mediterranean admixture. Some members of the family migrated to Canada in the 1880's and the last 4 generations have made their home in Michigan. The family pedigree is given in Figure 3. Typical examples of the familial anemia were first noted about 1810 in Holland when in 1 family (3) 6 male children died in infancy of pallor and bloodlessness.* The 2 female children were healthy and survived. The older daughter in later years had, in addition to her 7 apparently healthy female children, 2 anemic sons. One of them was pale and sickly all his life but lived to the age of 17 years. In the next generation 3 male infants died of the anemia when between 2 and 6 months old. The oldest child in this sibship (5-1), the grandmother of the 2 living anemic boys (17-7 and 17-10), was the oldest living individual in the family and she was available for examination. Her case history, those of her descendants and collaterals follow.

L. G. (5-1). This 65 year old grand-

mother had always had good general health without unusual illnesses. She had never been jaundiced and had had no chills, fever or known anemia. Physical examination on Nov. 6, 1944, showed pronounced obesity. There was no icterus and her liver and spleen could not be palpated. The peripheral blood counts and values were normal (Table 2). The red blood cells varied slightly beyond normal in size, but they were well and uniformly filled with hemoglobin. Four % of them were pale cells, oval in shape, similar to those in her daughter's blood (Fig. 4, A).

A. P. (6-1), the 66 year old husband of L. G. (5-1), was of French origin and had always enjoyed good general health. There were no known blood diseases in his family and there was no consanguinity. Physical examination disclosed no abnormalities and there was nothing unusual in the hematologic findings (Table 2).

Seven children were born to these parents. The oldest child (7-1), a boy, was pale and weak from the time of his birth. He was never well but lived to be 13 years of age when he died of "starvation of the blood." The third and fifth children were males who died of the anemia at about 4 months and 2 months of age, respectively. The seventh child died at birth, the cause of death being unknown. The 3 remaining children were living and examined.

M. P. M. (7-2). This 45 year old woman had had fairly good general health. In her teens she had several episodes of fever and later developed an acute arthritis of several months duration. After bearing several viable children she had 3 miscarriages and developed some gynecologic symptoms which finally led to a laparotomy and the removal of an ovarian cyst. Physical examination showed apparent good health. There was no jaundice and her liver and spleen were not palpable. The peripheral blood values were not definitely abnormal. The erythrocytes varied slightly beyond normal in size and 6% of them were the pale, thin, oval cells.

Her husband and 4 of their 5 living children were available for examination. All were normal except for 2 of the daughters who had the same minor blood abnormality

* We are indebted to Dr. T. B. Cooley for information regarding sibships 1, 2 and 3. The children in sibship 17 were under his care for a number of years.

TABLE 2.—SUMMARY OF BLOOD FINDINGS IN FAMILY II

Identity	Age, sex	Hb. (gm. per 100 cc.)	RBC (mill. per c.mm.)	Hemato-crit	M.C.V. (μ .)	M.C.H. (μ g.)	M.C.H.C. (%)	Morphology of RBC	Reticulo-eyte (%)	Range of hemolysis in hypotonic NaCl solutions	Blood type	Other findings
L. G.	65	14.6	4.7	42.0	89	31.0	34.8	Anisocytosis +, oval cells 4%	1.0	...	A ₁ MN	
L. G. 5-1	F							Normal	OMN	
A. P.	66	15.4	4.9	47.0	96	31.4	32.8			...	OMN	
A. P. 6-1	M							Anisocytosis +, pale, oval cells 6%	2.0	...	OMN	
M. P. M. 7-2	44 F	13.0	4.0	38.0	95	32.5	34.2		1.1	...	BMN	
V. M. A. 15-2	21 F	13.6	4.6	43.0	94	29.5	31.6	Anisocytosis +, pale, oval cells 10%	2.0	...	A ₁ MN	Spleen palpable
F. M. S. 15-3	20 F	12.8	4.4	37.0	84	29.1	34.6	Anisocytosis + +, pale, oval cells 20%	A ₂ MN	
L. E. P. 7-4	44 M	14.9	5.2	44.5	85	28.6	33.4	Normal	1.2	0.55-0.45 0.55-0.40*	ON	Splenomegaly
R. P. C. 7-6	39 F	14.8	4.5	42.5	95	32.8	34.8	Anisocytosis +, pale, oval cells 3%	..	0.55-0.35 0.55-0.40*	BMN	
J. C. 9-1	43 M	14.9	5.4	46.0	85	27.6	32.4	Normal	BN	
D. J. C. 17-6	14 F	13.0	4.8	40.0	84	27.0	32.4	Normal	1.6	0.55-0.15 0.50-0.40*	OMN	Splenomegaly, hepatomegaly
R. C. 17-7	13 M	7.0	5.5	27.0	49	12.7	25.9	Anisocytosis + + + +, poikilocytosis + + +	1.0	...	BN	Splenomegaly
M. M. C. 17-8	12 F	13.1	4.3	38.0	88	30.2	34.5	Anisocytosis + +, pale, oval cells 10%	5.0	0.50-0.20 0.50-0.40*	BMN	Past splenectomy
J. C. 17-10	9 M	5.6	2.8	20.0	71	20.0	28.0	Nucleated RBC, anisocytosis + + + +, poikilocytosis + + +	..	0.50-0.40 0.55-0.40*	OMN	Palpable spleen
G. C. 17-11	9 M	13.2	5.5	41.0	75	24.0	32.2	Normal	BMN	
E. C. 17-13	6 M	13.6	5.2	40.0	77	26.1	34.0	Normal	ON	
M. C. 17-14	4 M	13.1	5.2	39.0	75	25.1	33.6	Normal		

* Normal control.

as their mother, and in 1 of them the spleen was palpable. Their case histories follow.

V. M. A. (15-2), the 21 year old married daughter of M. P. M. (7-2), had an acute type of arthritis at the age of 4 years, but afterward she was well. Her first child died 5 hours after delivery by Cesarean section and her second pregnancy ended in a spontaneous miscarriage at 3 months gestation.

at 10 years of age, and an operation for "suspending" the uterus at the age of 19 years. Her one pregnancy had terminated a few weeks previously in a spontaneous miscarriage after 4½ months gestation. Physical examination showed good general development. Her liver was not palpable. A slender spleen was palpable well below the costal margin deep in the left upper

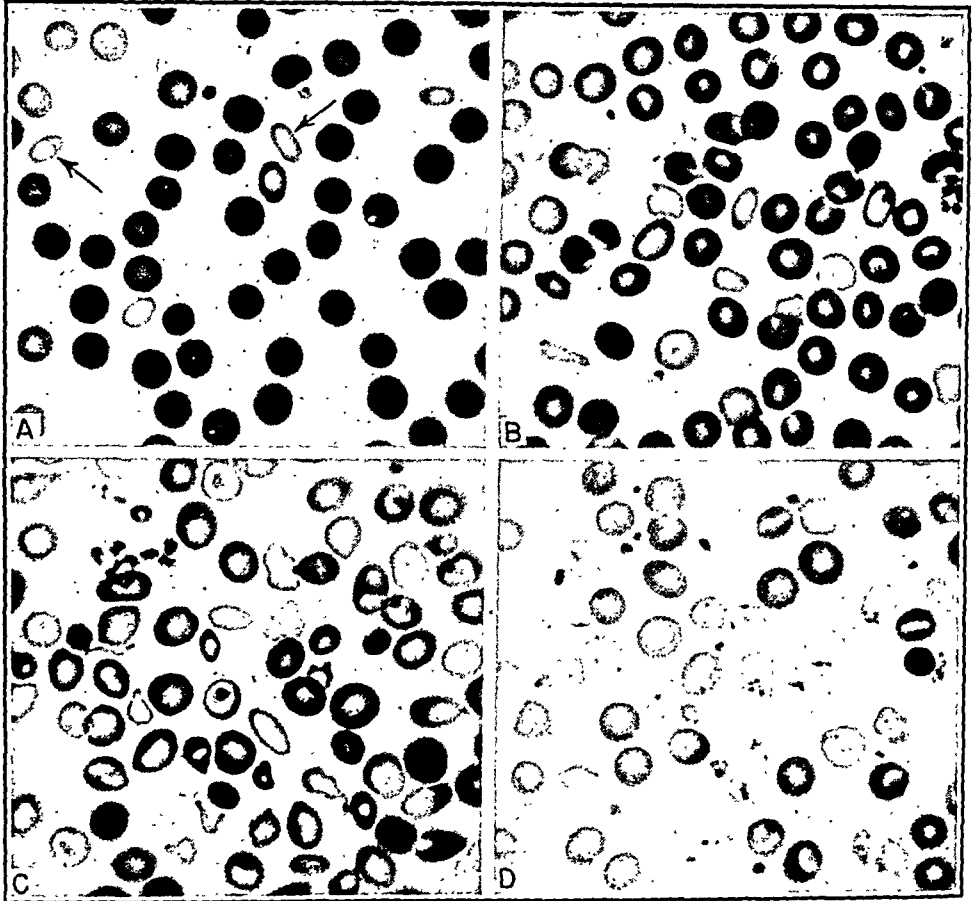


FIG. 4.—Stained blood films of members of Family II. A, R. P. C., 7-6. Five of the pale, oval cells are seen in the field and 2 of them are indicated by arrows. B, F. M. S., 15-3; C, R. C., 17-7; and D, J. C., 17-10.

Physical examination showed no abnormalities and neither the liver nor the spleen was palpable. The peripheral blood values were normal. Many of the erythrocytes varied beyond normal in size, in shape, and in hemoglobin content and 10% of the cells were the small, pale, oval type.

F. M. S. (15-3). This 20 year old married sister of V. M. A. (15-2) had enjoyed good general health in spite of an unusual number of childhood diseases, an appendectomy

quadrant of the abdomen, but it did not seem to be definitely larger than normal.

The peripheral blood values were not unusual. The stained red blood cells, however, were definitely abnormal in morphology, showing excessive variability in size, in shape, and in hemoglobin content with 20% of them being the small, oval and pale cells (Fig. 4, B). A rare cell contained several tiny, darkly stained inclusions.

L. E. P. (7-4). This 44 year old male

had always been well. He had never been jaundiced, nor had chills or fever. Physical examination showed no abnormalities other than an inguinal hernia. The liver and spleen were not palpable. The blood values and the erythrocyte morphology were normal.

R. P. C. (7-6) was the 39 year old mother of the 2 living anemic boys (17-7 and 17-10), and she had never been seriously ill. At the age of 15 years she had hypermenorrhea and was thought to be anemic at that time. She had never been jaundiced nor had she chills or fever. Following her fifteenth pregnancy relaxation of the pelvic floor was corrected by a hysterectomy and a plastic operation. Physical examination showed no abnormalities other than an enlarged spleen which filled much of the left upper quadrant of the abdomen, the broad tip of it descending 2 to 3 cm. or more below the costal margin at the beginning of inspiration. The peripheral blood values were normal. The red blood cells varied slightly in size and in hemoglobin content; 3% of them were small, pale, oval cells (Fig. 4, A).

J. C. (9-1), the 43 year old husband of R. P. C., had had no serious illness and he was in good general health. There was no consanguinity. Physical examination and a complete blood examination revealed no abnormalities.

J. C. C. (17-1). At birth this boy appeared to be a normal infant and weighed 6½ pounds. After a few days he gradually became pale, weak, ate poorly and lost weight. Coughing and vomiting developed and he died when 3 months and 7 days old.

L. W. C. (17-2). This boy was always well and at the age of 18 years began service in the U. S. Navy. He was not available for examination.

R. M. C. (17-3). Until the age of 7 years this girl was healthy but she then contracted rheumatic fever. She died of cardiac failure 2 years later.

J. C. (17-5). This male infant had the exact symptoms and clinical course as 17-1 and died of the anemia when 3 months and 8 days old.

D. J. C. (17-6) was a 14 year old school-girl who had always enjoyed robust health. A physical examination and a complete blood examination showed no abnormalities.

R. C., No. 543696 (17-7). This 13 year old schoolboy was first seen at the Simpson

Memorial Institute on March 13, 1944. His general health had never been more than fairly good. At birth he appeared to be normal and weighed 6 pounds. After a few weeks, however, like the 2 previous male infants, he began to eat poorly and became extremely pale. At the age of 3 months the family physician discovered that his hemoglobin was 10% of normal and did not expect him to live. A variety of hormone preparations were administered and he began to improve slowly. After the age of 1 year he had no serious symptoms but he was never strong or vigorous. Common illnesses affected him severely and convalescence was often prolonged. When 11 years old he began to work after school hours and he soon became weak and generally ill. One blood transfusion was required at that time before he began to regain his usual degree of health.

Physical examination showed him to be fairly well developed and somewhat underweight. His face was pale and pudgy but there was no icterus. His heart was at the upper limits of normal in size. The spleen was enlarged to fill the left upper quadrant of the abdomen, with the inferior margin being palpable 4 cm. below the left costal margin. The liver edge was felt 2 to 3 cm. below the margin of the ribs on the right side. No other physical abnormalities were found.

Roentgen examination of the skull, chest, spine and hands showed no bony abnormality.

Examination of the peripheral blood (Table 2) showed the presence of a severe hypochromic microcytic anemia. Nearly half of the red blood cells were oval and all of them varied to extreme degree in size, in shape, and in hemoglobin content (Fig. 4, C). There was no change in erythrocyte morphology in fresh sealed preparations after 48 hours. Target cells numbered 0.3% and reticulocytes 1.6%. A rare cell contained several tiny darkly stained inclusions. A hypotonic saline fragility test showed increased resistance of the erythrocytes to hemolysis. The white blood cell and differential counts were normal.

He was seen at intervals for several months during which time his general condition and his blood status remained unchanged.

M. M. C. (17-8) was a 12 year old school-

girl who had had only the common childhood diseases and her general health was good. Physical examination showed no abnormalities except an easily palpable spleen, the tip of which lay 1 cm. or so below the left costal margin at the beginning of inspiration. The peripheral blood values were not abnormal. In the stained blood films the red blood cells varied beyond normal in size and in hemoglobin content. Ten % of the erythrocytes were small, oval and extremely pale.

J. C., No. 543350 (17-10). This 9 year old boy was admitted to the Simpson Memorial Institute on April 3, 1944. He was one of dissimilar twins and he had never been well. At birth he appeared to be a healthy infant of about average weight. After a few weeks he became pale, sickly, and ate poorly as had the other afflicted male children in his family. With the onset of these symptoms his diet was supplemented with cod liver oil, cooked and powdered liver, and tomato juice. After a few months he gradually improved and for 3 or 4 years he was reasonably healthy. When 5 years of age he suffered a minor cut with trauma to his knee and shortly afterward he became very pale and generally ill. He was taken to his local hospital where an enlarged spleen and a severe anemia were found. The blood values did not improve with the prolonged administration of many liver, iron and vitamin preparations, and blood transfusions at regular intervals became necessary to keep him alive. Nearly 50 transfusions were given during the next 4 years. One year before admission his spleen was removed at the Children's Hospital in Detroit. This resulted in no improvement and, if anything, his blood values dropped faster than before the operation. He continued to tire easily and vigorous activity could not be tolerated. Jaundice, chills and fever had never occurred.

Physical examination at the time of admission showed him to be pale and underdeveloped but well nourished. His face appeared pudgy but not mongoloid. There was no icterus. His heart was slightly enlarged and a moderately loud systolic murmur was audible at the apex. There was a well-healed splenectomy scar in the left upper abdominal wall. The liver edge could not be palpated and the area of hepatic dullness was not increased. The

remainder of the physical examination disclosed no abnormalities.

Urinalysis and a stool examination were normal. The serum bilirubin was 0.5 mg. per 100 cc. and the urine urobilinogen excretion was not increased. The cephalin flocculation test of hepatic function was 2+ positive. Roentgen films of the chest confirmed the slight cardiac enlargement and additional films of the skull, spine and hands showed no skeletal abnormality.

The peripheral blood values (Table 2) were those present 7 weeks after he had been transfused with 785 cc. of red blood cells. In the stained films, about 40% of the cells appeared to be donor's cells. The patient's erythrocytes were extremely thin and many contained so little hemoglobin as to be nearly invisible (Fig. 4, D). There was extreme variability in size and shape, and the majority contained tiny Howell-Jolly bodies in addition to inclusions similar to those described by Pappenheimer, Thompson, Parker and Smith.³¹ Six % were target cells and 5% were reticulocytes. There were 65 nucleated erythrocytes for every 100 white blood cells. The number of platelets was greatly increased. The white blood cell count, when corrected for the number of nucleated red cells present, was normal. The appearance of the stained white cells and the differential count were normal, without myeloid immaturity being present. After a series of blood transfusions had been given nucleated red blood cells became rare. It was said that the red blood cell morphology before his splenectomy was identical with that of his brother, R. C. (17-7).¹⁰

G. C. (17-11) was the 9 year old dissimilar twin of J. C. (17-10). He had always been small in stature but in excellent health. He had had no unusual illnesses or symptoms. Physical examination showed no definite abnormalities although the tip of the spleen was palpable 1 cm. below the left costal margin at the end of deep inspiration. The blood values and cellular morphology were not abnormal.

E. C. (17-13) and M. C. (17-14) were healthy boys, 6 and 4 years old, respectively. Physical examinations and blood examinations showed no abnormalities. J. C. (17-15), the youngest child, was a healthy infant who died at the age of 1 year of pneumonia.

During the course of this study we have encountered at least 4 additional patients, unrelated to the 2 families just described, who had chronic types of refractory anemia resembling those of known hereditary origin. They presented much the same type of clinical problem as the white woman of non-Mediterranean origin reported by Valentine and Neel,⁴² who had a chronic hypochromic anemia refractory to iron therapy that showed many of the characteristics of thalassemia minor. The blood of both of her parents was normal and the hereditary nature of the blood disorder could not be proved. One of our patients (D. C., No. 543866) was a 22 year old white housewife whose ancestors were of northern European stock. A severe anemia was discovered during her first pregnancy and this was again found to be present after a febrile illness. No frank symptoms of anemia were ever present. During the 6 months prior to our examination her red blood cell count ranged between 2,800,000 and 3,410,000 per c.mm., and the hemoglobin between 36 and 67% of normal, despite 9 blood transfusions and many injections of liver extract.

Physical examination showed that there was no icterus and neither the liver nor the spleen was enlarged. Roentgenograms of the skeleton showed no abnormality. Examination of the peripheral blood 4 days after the last blood transfusion (Table 3) showed that a normocytic anemia was still present and that her erythrocytes varied far beyond normal in size and in hemoglobin content. There was no increase in reticulocytes. The white blood cell count was 4300 per c.mm., and of these 2% were myelocytes, 2% metamyelocytes, 0.5% hemohistocytes. The sternal marrow was less cellular than normal but it contained abundant normoblasts, fewer erythroblasts, and not infrequent megaloblasts. The erythroid cells outnumbered the myeloid cells 4 to 1. The blood transfusions were discontinued and she remained in good health during the following year. A second blood examination showed slightly improved blood values and at this time there was no immaturity of the myeloid cells. The blood of several relatives was examined and her mother was found to have a hypochromic microcytic anemia (Table 3) with disproportionately deformed red blood cells.

A second patient (M. E., No. 340785), a woman of middle European ancestry, was 26 years of age when she was first seen for consultation regarding a chronic anemia. She had been free of infection, had had no unusual blood loss and had never been icteric. There were no physical abnormalities other than that her spleen was palpable just below the costal margin. The blood bilirubin was 0.59 mg. per 100 cc. A gastric analysis showed average amounts of free hydrochloric acid. A hypochromic, microcytic anemia was present with an unusual degree of red blood cell distortion (Table 3). There was no improvement in the blood status after many courses of iron therapy, liver and vitamin preparations, etc. The blood values fluctuated but little over an observation period of 10 years. No members of her family were available for investigation.

A third patient (L. U., No. 266609) was a male of non-Mediterranean origin, 36 years of age when he was first seen in 1931, a few weeks after chronic fatigue and a yellowish complexion led to the discovery of a severe anemia with conspicuous red blood cell malformation (Table 3). At that time the only physical abnormality was slight enlargement of the spleen. There was no evidence of blood loss. After 3 months treatment with iron and other medications the red blood cell count rose to 4,400,000 while the hemoglobin remained between 50 and 64% (Sahli). There was little change in erythrocyte morphology. He enjoyed fairly good general health during the next 11 years but following a febrile illness early in 1943 a severe anemia recurred (Table 3). Physical examination showed that there was no jaundice. The spleen had enlarged slightly more to become palpable 3 cm. below the costal margin at respiratory rest. The blood bilirubin was 0.5 mg. per 100 cc. There was no improvement with several types of anti-anemic therapy, oral and intravenous iron, liver extract injections, etc., and repeated series of blood transfusions became necessary. Five months later an exploratory laparotomy was advised since a number of stools had given positive guaiac tests. At operation the abdominal organs appeared grossly normal and no source of intestinal bleeding was found. It was decided to remove the spleen and a biopsy of the liver was taken.

The blood values gradually improved for a time but the red blood cells became even more bizarre in size and shape with about 40% of them containing Howell-Jolly bodies or minute inclusions (Table 3). His clinical condition did not improve, however, and he died in July 1944, 1 year after the splenectomy. Pathologic examination of the spleen, the liver tissue removed by biopsy, and the organs removed at autopsy showed extensive deposit of golden brown

largely confined to individuals with some variety of hereditary anemia.^{1,2,5,29,31,36,39}

A fourth patient (A. E. S., No. 276728) was a 64 year old laborer born in Michigan. His family was of British extraction without known Mediterranean ancestry. He was treated at the University Hospital in 1931 for carcinoma of the lip and from 1941 to 1945 for recurrent peptic ulceration with hemorrhage. During the later admissions abnormally shaped red blood cells were observed, but

TABLE 3.—BLOOD FINDINGS IN CASES OF ATYPICAL ANEMIA RESEMBLING THOSE OF HEREDITARY ORIGIN

Patient	Age, sex	Hb. (gm. per 100 cc.)	RBC (mill. per c.mm.)	Hemato- crit	M.C.V. (cμ.)	Reticulo- cyte (%)	Morphology of RBC
D. C., No. 543866	22 F	(3/16/44) 9.9	3.6	31.5	87	1	Anisocytosis ++, poikilocytosis +, oval cells 15%, rare nucleat- ed RBC
		(2/21/45) 11.2	3.8	35.5	93	..	Unchanged
J. E. (mother of D. C.)	52 F	8.8	4.7	32.0	68	1	Anisocytosis ++, poikilocytosis +, oval cells 15%
M. E., No. 340785	26 F	7.8 to 10.7	3.6 to 5.0	29.0 to 36.5	54 to 68	2	Anisocytosis ++, poikilocytosis ++, tar- get cells, pencil, frag- mented and stippled cells present
L. U., No. 266609	36 M	(6/9/31) 7.5	2.8	No incr.	Poikilocytosis + + + +, many pencil cells
		(2/21/43) 3.0	1.8	11.0	62	2	Anisocytosis ++, poikilocytosis + + +, spindle and pencil cells
		(12/2/43) 8.8	4.9	30.5	62	2.5	Anisocytosis + + + +, poikilocytosis + + + +, fragmented and pencil cells, target cells 8%, cells with Howell-Jolly bodies 40%
A. S., No. 276728	64 M	13.1	5.7	45.0	79	..	Anisocytosis + + +, poikilocytosis + + + +, spindle, racquet and pencil cells abundant

pigment which with special staining was shown to contain abundant iron. The pathologic findings were said to resemble closely those of hemochromatosis as do those in erythroblastic anemia.⁴³ The blood findings throughout life were compatible with an hereditary type of anemia, but no relatives were examined. The conspicuous alteration in the red blood cell morphology following splenectomy may be of diagnostic significance since these changes have been

the anemia associated with the gastro-intestinal bleeding always responded to iron therapy. The erythrocyte deformity persisted, however, with the return to normal blood values (Table 3). There was no hepatomegaly or splenomegaly and he was never icteric. There was no knowledge of blood abnormalities in other members of his family but an investigation of them has not yet been carried out.

Discussion. A hypochromic microcytic anemia, with irregularly shaped red blood cells varying greatly in hemoglobin content, splenomegaly and sometimes hepatomegaly has been observed to recur in 2 families through several generations. A noteworthy feature of the anemia in these families is its restriction to those of the male sex. In one family the disease becomes manifest early in life and usually terminates fatally at an age of 4 to 6 months. Only a few of the afflicted males live to puberty. In the other family symptoms of anemia did not appear in 1 case until there was apparently an episode of acute erythrocyte hemolysis at the age of 29 years. A younger brother who was afflicted appeared well and healthy at the age of 15 years, and the degree of his anemia, erythrocyte abnormality, and splenomegaly was less at that age. The physical and blood findings in the case of their $3\frac{1}{2}$ year old nephew appeared to be significantly abnormal and it is possible that in later life he will develop a similar anemia. Only through repeated observations through the years, however, will the eventual prognosis in the latter family be established and the appearance of the disorder at different periods of life be determined.

The anemia appears to be transmitted from generation to generation by 1 parent only and follows a pattern compatible with sex-linked inheritance in which the character is recessive, or incompletely recessive, in females. Anemia was not found in any of the females, even in those who were known to have transmitted the disease to their sons, but several of them could be recognized as carriers of the disease trait by the presence of an enlarged spleen or by certain erythrocyte abnormalities. In Family I the mother, R. F. P. (6-3), of the 2 anemic males was certainly a carrier of the trait and she had a definitely enlarged spleen. Her peripheral blood values were normal and her red blood cells showed excessive variation in size. Four other females in the family (6-2, 6-4, 11-2, and 17-1) were

thought probably to be carriers of the anemic trait because of similar minor erythrocyte abnormalities with 1 of the women having in addition a demonstrable splenomegaly. Roentgen examination of the 3 women without palpable spleens, 1 of whom was very obese, might have disclosed enlargement of the spleen but these procedures were not feasible.

In Family II, both L. G. (5-1) and R. P. C. (7-6) transmitted the anemia to their children. Their carrier state could be established more easily and with more certainty than in the other family by a greater variation in size and in hemoglobin content of their erythrocytes and by the presence among them of small, pale, oval cells. R. P. C. (7-6) had in addition a definitely enlarged spleen which obesity might have obscured in L. G. (5-1). Four other females in this family (7-2, 15-2, 15-3 and 17-8) had similar erythrocyte abnormalities and were thought also to be carriers of the anemic trait. None of them were anemic and in 2 cases the spleen was palpable. The number of small, pale, oval red blood cells in their blood ranged from 6 to 20%. These erythrocyte abnormalities were more conspicuous in the younger women and most pronounced in F. M. S. (15-3) who had recently had a miscarriage after $4\frac{1}{2}$ months gestation. The effect of pregnancy, infection, and blood loss in these individuals was not studied further. The possible relation of the carrier state to the frequent miscarriages is difficult to evaluate, particularly since the sex of the fetuses was not recorded.

R. F. P. (6-3) in Family I and both L. G. (5-1) and R. P. C. (7-6) of Family II had normal sons as well as anemic sons, thus proving themselves to be heterozygous for the gene responsible for the anemia. M. P. M. (7-2) in Family II had a normal daughter, 2 carrier daughters, and 1 normal son and likewise appears to be heterozygous. The other females showing evidence of being carriers of the abnormal gene may be presumed to be heterozygous, also.

Sex-linkage, a relatively common type of human inheritance, in our opinion, appears to be the most likely genetic mechanism operating in the inheritance of the anemia in these families. Another less frequent mode of heredity is possible, however, that of an autosomal dominant character reaching full expression in males and being incompletely recessive in females. Sex-linked inheritance can be distinguished from autosomal sex-limited or sex-influenced inheritance only by the study of descendants of affected males. Unfortunately only 1 such male, 2-3 in Family I, had offspring. His 1 son was normal as would necessarily be the case if the disease were sex-linked; but if it were autosomal and dominant the son would have had only an even chance of being normal. All female children of such individuals in sex-linked inheritance would be carriers of the trait, as indeed his 3 daughters appeared to be. This could occur by chance, of course, if the inheritance were autosomal and dominant. To determine whether the anemia could reach its full expression in females, homozygous individuals from matings between female carriers and affected males would be necessary. Such matings did not occur in either family and, therefore, there is no information on this point. Study of the results of the various heredity test factors, color vision, blood types, secretor factor, etc., were consistent with the stated paternity relationships but failed to indicate any evidence of genetic linkage between them and the anemia being studied. Final proof of the genetic linkage of the hereditary anemia in these families must await the study of future generations.

The 2 families described here are the first ones reported in which a sex-influenced or sex-linked anemia has been found. In the other hereditary anemias the mode of inheritance is different. In sickle cell anemia and in familial hemolytic icterus males and females are affected alike and either sex may transmit the disease to their children.^{12,17,21,38} Recent studies of families with Mediterranean anemia indi-

cate that this anemia occurs roughly in 2 grades of severity, in a mild usually asymptomatic form "thalassemia minor," and in a severe usually fatal form, "thalassemia major" or Cooley's anemia. When the parents of children with thalassemia major are studied, significant blood abnormalities have been present in nearly every case in both parents.^{23,28,34,35,42,44} It is thought that the carrier state, thalassemia minor, is due to heterozygosity for a factor which when homozygous results in the severe anemia, thalassemia major.⁴² This is of interest in comparison with the inheritance of elliptocytosis in non-Mediterranean races. Elliptic red blood cells are found with equal frequency in males and in females and the anomaly is transmitted by both sexes as a simple dominant characteristic.^{3,7,14,22,26,36,45} The majority of individuals with elliptic erythrocytes are not anemic but healthy, long lived, and not unusually subject to disease. One instance of a mating between 2 individuals both having elliptic red cells has been recorded.⁴⁵ One female child of these parents developed a hypochromic anemia with splenomegaly, a positive indirect van den Bergh reaction, greatly increased red cell fragility, reticulocytosis and spherocytosis. A history of having had hemolytic crises with icterus was obtained. This severe hemolytic tendency may indicate the results of homozygosity for the elliptic cell trait. Other cases of splenomegaly and jaundice in elliptic cell bearers have been reported,⁴⁵ and Leitner²⁷ has recently studied another family in which this occurs.

The hematologic features of the hereditary, sex-linked anemia are more comparable to those of severe Mediterranean anemia than to any other recognized entity. The degree of hemoglobin deficiency, the microcytosis and conspicuous red blood cell malformation is similar in both conditions. Erythroblastosis was not seen in those with sex-linked anemia, however, except in 1 case in which it followed splenectomy. There was decreased erythrocyte fragility in hypotonic

saline solutions as might be anticipated with the degree of red cell distortion present. The ordinary anti-anemic measures proved to be of no therapeutic value, and in 1 case splenectomy, as in Cooley's anemia, was of no benefit. Several features may be cited which serve to differentiate the 2 types of anemia. Leukocytosis with immaturity of the myeloid cells, common in Mediterranean anemia, was not seen in any of the individuals with sex-linked anemia and evidence of increased red cell hemolysis, icterus, increased blood bilirubin and urobilinogen excretion, or high reticulocytosis was minimal or absent in all of the anemic males studied. Roentgenograms of the skeleton in those with the sex-linked anemia showed none of the abnormalities so characteristic of Mediterranean anemia when it is present in comparable severity.^{2,6,20,43} The degree of splenomegaly and hepatomegaly, also, is far less in the sex-linked anemia than in similarly severe Mediterranean anemia. The difference in the genetic transmission of the 2 types of anemias has already been discussed.

A general classification or final description of the hereditary anemias is far from possible at this time. Evidence is accumulating to show that inherited abnormalities of erythrocyte formation or of hemoglobin production are probably more common than generally recognized.⁴ A disorder of this type should be considered in diagnosis when in an otherwise healthy individual a hypochromic anemia does not respond to iron therapy, or where

there is an unusual degree of red cell malformation with or without splenomegaly, hepatomegaly, or evidence of increased hemolysis. Errors in diagnosis may be made when such refractory anemias are attributed to chronic blood loss which cannot readily be demonstrated or patients may be unjustly accused of failing to take the prescribed iron medication. The hematologic findings are seldom entirely pathognomonic of an hereditary disorder, however, and examinations of other members of the family group, especially the parents, are often necessary before the etiology is entirely clear. In such investigations it may be anticipated from the heredity standpoint that a disorder having a given clinical appearance (phenotype) may be found to vary in its genetic basis of transmission (genotype) in different families or in different racial groups.

Summary. A hypochromic microcytic anemia with deformed erythrocytes, splenomegaly and sometimes hepatomegaly, affecting the male members of 2 families through several generations, has been described. The disease appears to be transmitted from generation to generation by females, many of whom have enlarged spleens and minor red blood cell abnormalities without anemia, in a manner compatible with sex-linked inheritance in which the abnormality is recessive, or incompletely recessive, in females.

The general problem of the atypical hereditary anemias is discussed.

REFERENCES

1. ALLEN, E. G., and CHILDS, D. S.: *New York State J. Med.*, **36**, 641, 1936.
2. BATY, J. M., BLACKFAN, K. D., and DIAMOND, L. K.: *Am. J. Dis. Child.*, **43**, 667, 1932.
3. BERTELSEN, A.: *Ugesk. f. Læger*, **100**, 136, 1938.
4. BETHELL, F. H., STURGIS, C. C., RUNDLES, R. W., and MEYERS, M.: *Arch. Int. Med.*, **76**, 358, 1945.
5. BYWATERS, E. G. L.: *Arch. Dis. Child.*, **13**, 173, 1938.
6. CAFFEY, J.: *Am. J. Roentgenol.*, **37**, 293, 1937.
7. CHENEY, G.: *J. Am. Med. Assn.*, **98**, 878, 1932.
8. COOLEY, T. B., and LEE, P.: *Trans. Am. Pediat. Soc.*, **37**, 29, 1925.
9. COOLEY, T. B.: *Am. J. Dis. Child.*, **62**, 1, 1941.
10. COOLEY, T. B.: *AM. J. MED. SCI.*, **209**, 561, 1945.
11. DAMESHEK, W.: *AM. J. MED. SCI.*, **205**, 643, 1943.
12. DEBRÉ, R., LAMY, M., SÉE, G., and SCHRAMMECK, G.: *Am. J. Dis. Child.*, **56**, 1189, 1938.
13. FANCONI, G.: *Arch. f. Kinderh.*, **117**, 1, 1939.
14. FLORMAN, A. L., and WINTROBE, M. M.: *Bull. Johns Hopkins Hosp.*, **63**, 209, 1938.

15. FOSTER, L. P.: *Am. J. Dis. Child.*, **59**, 828, 1940.
16. FREUDENBERG, E., and ESSER, M.: *Ann. Pediat.*, **153**, 128, 1942.
17. GANSSLEN, M., ZIPPERLEN, E., and SCHÜZ, E.: *Deutsch. Arch. f. klin. Med.*, **146**, 1, 1925.
18. GIFFIN, H. Z., and WATKINS, C. H.: *Trans. Assn. Am. Phys.*, **54**, 355, 1939.
19. GOLDHAMER, M. L.: *Ohio State Med. J.*, **38**, 321, 1942.
20. GRINNAN, A. G.: *Am. J. Roentgenol.*, **34**, 297, 1935.
21. HANSEN, K., and KLEIN, E.: *Deutsch. Arch. f. klin. Med.*, **176**, 567, 1934.
22. HJLMANS VAN DEN BERGH, A.: *Arch. f. Verdauungskr.*, **43**, 65, 1928.
23. INTROZZI, P.: *Hæmatologica*, **16**, 525, 1935.
24. LAMBRECHT, K.: *Ergebn. d. inn. Med. u. Kinderh.*, **55**, 295, 1938.
25. LAWRENCE, J. S.: *Am. J. Med. Sci.*, **181**, 240, 1931.
26. LEITNER, S. J.: *Deutsch. Arch. f. klin. Med.*, **183**, 607, 1939.
27. LEITNER, S. J.: *Helvet. med. Acta*, **10**, 585, 1943.
28. MICHELI, F., PENATI, F., and MOMIGLIANO LEIN, G.: *Hæmatologica*, **16**, 5 (Suppl.), 1935.
29. MILLER, J. K., and LUCAS, M. A.: *Am. J. Clin. Path.*, **8**, 391, 1931.
30. NAPIER, L. E., SHORTEN, J. A., and DAS GUPTA, C. R.: *Indian Med. Gaz.*, **74**, 660, 1939.
31. PAPPENHEIMER, A. M., THOMPSON, W. P., PARKER, D. D., and SMITH, K. E.: *Quart. J. Med.*, **14**, 57, 1945.
32. VAN RAVENSWAAY, A. C., SCHNEPP, K. H., and MOORE, C. V.: *J. Am. Med. Assn.*, **122**, 83, 1943.
33. ROHR, K.: *Helvet. med. Acta*, **10**, 31, 1943.
34. SMITH, C. H.: *J. Pediat.*, **20**, 370, 1942.
35. SMITH, C. H.: *Am. J. Dis. Child.*, **65**, 681, 1943.
36. STEINBRINCK, W., and HAHNELT: *Deutsch. med. Wchnschr.*, **64**, 784, 1938.
37. STEPHENS, D. J., and TATELBAUM, A. J.: *J. Lab. and Clin. Med.*, **20**, 375, 1935.
38. STRANDSKOV, H. H.: *Physiol. Rev.*, **24**, 445, 1944.
39. STRANSKY, E., and REGALA, A. C.: *Am. J. Dis. Child.*, **63**, 859, 1942.
40. STRAUS, M. B., and DALAND, G. A.: *New England J. Med.*, **217**, 100, 1937.
41. STRAUS, M. B., DALAND, G. A., and FOX, H. J.: *Am. J. Med. Sci.*, **201**, 30, 1941.
42. VALENTINE, W. N., and NEEL, J. V.: *Arch. Int. Med.*, **74**, 185, 1944.
43. WHIPPLE, G. H., and BRADFORD, W. L.: *J. Pediat.*, **9**, 279, 1936.
44. WINTROBE, M. M., MATTHEWS, E., POLLACK, R., and DOBYNS, B. M.: *J. Am. Med. Assn.*, **114**, 1530, 1940.
45. WYANDT, H., BANCROFT, P. M., and WINSHIP, T. D.: *Arch. Int. Med.*, **68**, 1043, 1941.

BLOOD CHANGES RELATED TO SULFONAMIDE THERAPY

I. APLASTIC ANEMIA ASSOCIATED WITH SULFONAMIDE THERAPY

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APLASTIC anemia as discussed in this report is regarded as a disease entity in which granulocytopenia, marked anemia and thrombocytopenia are associated with hypoplasia of the bone marrow. The rarity of the condition is evidenced by the paucity of reported cases. The disease occurs chiefly in young adults in a good state of nutrition, is refractory to treatment with any of the accepted hemato-poietic agents and is invariably fatal except in some of the secondary group. Aplastic anemias are divided into 2 groups, idiopathic and secondary; the secondary group may be on an infectious, toxic or chemical basis. Six cases of aplastic anemia are reported here. In 5 of the patients there was a definite history of relationship to sulfonamide therapy and in the 6th the autopsy findings were indicative of similar therapeutic association. In 4 of the cases the clinical diagnosis was confirmed by autopsy findings. Arsenicals, Roentgen ray and ultraviolet radiations, gold preparations, phenol and sulfonamide drugs are the most common therapeutic agents producing this anemia, and benzene, toluene, anilin dyes and poisonous gases have also been implicated. Arsenical and benzene compounds have been the etiologic factors in the majority of the recorded cases. Blood dyscrasias are among the less frequently observed pathologic changes produced by the sulfonamides and include hemolytic anemia, aplastic anemia, granulocytopenia and purpura. Granulocytopenia associated with sulfonamide therapy will be discussed in the following paper. A moderate number of

hemolytic anemias associated with sulfonamide therapy in adults has been recorded, but aplastic anemia due to these drugs has been uncommon and we have found only 3 cases in the literature. In 1942, Meyer and Perlmutter² reported the development of aplastic anemia in a 55 year old female following the administration of 12 gm. of sulfathiazole in the treatment of pneumonia. Discontinuance of the drug and repeated blood transfusions resulted in regeneration of the bone marrow, but the patient subsequently died of infection. Strauss³ in 1943 described an erythrocytic aplasia following the administration of 11 gm. of sulfathiazole in a colored female aged 55 years. After 5 blood transfusions there was regeneration of bone marrow and the patient recovered. Sutliff and associates⁴ investigating sulfonamide intoxication as a cause of death in New York City in 1941 reported 1 case of aplastic anemia among 8 deaths.

Pertinent data regarding the 6 patients who died recently from aplastic anemia in the Children's Hospital of Pittsburgh are outlined in the following pages.

Case Abstracts. CASE 1. J. G., a white 13 year old male, was admitted to this hospital on Sept. 8, 1943. Past medical history was not pertinent. Nine weeks before admission the boy had been lacerated in the right side by a pitchfork and was given antitetanic serum immediately. He became anemic and sulfathiazole and ferric sulfate were administered for 9 days at home without any improvement. He was then admitted to Greene County Memorial Hospital

of Waynesburg with a diagnosis of aplastic anemia. Roentgen rays of the chest were negative. Urinalyses and repeated blood cultures were negative. Between August 17 and 27, 27 gm. of sulfadiazine were given. On August 26, the stool showed occult blood. After 8 blood transfusions and intensive anti-anemic therapy the patient had not improved and on September 8 was transferred from the Waynesburg Hospital to this hospital. The chief complaints were bleeding from ulcerated gums and mouth, epistaxis,

(amount not obtainable) for 1 week. In the Waynesburg Hospital, 27 gm. of sulfathiazole were given.

At *autopsy* (3½ hours after death), the body showed small ulcerations and blood crusts around the mouth and nares. The subcutaneous tissues of the head, trunk and extremities were darkened with extravasated blood and petechiæ. On the right buttock, there was an abscess 6 cm. in diameter with 2 draining sinuses. Petechiæ were also present in the intercostal muscles, pleura,

TABLE 1.—BLOOD EXAMINATIONS

Patient	Date	Hb. (gm.)	RBC ^{10⁶}	WBC ^{10³}	% granu- locytes	Platelets ^{10³}	Other tests	Remarks
1. J. G.	7/15/43	4.5	1.3	2.0	39	86	In Waynesburg Hosp.
	7/30/43	7.0	2.0	2.0	46	89		
	8/30/43	5.0	1.5	1.0	9			
	9/ 8/43	4.9	1.1	1.1	3	44	Bleed. time 5', coag. time 6'	In Children's Hosp.
	9/16/43	3.5	1.2	2.1	3	..	No reticulocytes	
	9/18/43	3.8	1.1	0.9	No reticulocytes	Transfusions
L. B.	4/ 3/42	14.0	4.5	10.0	52	First admission
	2/28/43	13.5	4.1	22.0	67	Second admission
	9/ 8/43	5.2	1.5	1.1	3	51	Third admission
	10/ 1/43	2.6	0.8	1.3	3	Repeated transfusions
3. A. T.	12/ 3/42	3.7	0.9	5.5	56	215	Bleed. time 1.5', coag. time 10+	Repeated transfusions
	12/15/42	8.8	2.6	4.0	27	..	Fragility normal	
	12/31/42	11.3	3.5	9.0	17			
	1/19/43	10.0	4.0	5.2	7			
	1/30/43	8.0	2.7	1.8	4			
	2/ 1/43	6.9	2.3	0.9	3			
4. D. L.	1/ 8/45	*	0.8	2.2	15	66	Nucl. red cells, 41 to 100 WBC	
	7/ 9/45	13.0	4.1	5.6	50	Blood transfusions
5. J. M. R.	7/29/43	11.0	3.9	3.3	39	First admission
	8/10/43	9.5	3.0	3.9	14	Second admission
	8/16/43	12.8	4.4	1.4	46			
	11/23/43	2.7	0.9	0.7	15	54	Bleed. time 56", coag. time 4'	Third admission
	11/29/43	6.8	1.5	0.5	3			
6. A. Z.	7/31/44	6.2	2.1	2.7	11	60	Bleed. time 6', coag. time 3.5'	First admission, Uniontown Hosp.
	9/ 9/44	9.5	3.4	6.1	45			
	1/28/45	6.7	3.1	1.9	6	..	No reticulocytes, fragility normal	Second admission, Uniontown Hosp.
	3/ 3/45	8.5	2.6	2.1	32	18.6	In Children's Hosp.
	3/15/45	6.5	2.4	1.9	6			
	3/23/45	6.0	1.6	1.1	4	Repeated transfusions
	3/29/45	6.5	2.3	1.2	5			

* Too low to read.

blurred vision and subcutaneous hemorrhages. There were enlarged cryptic tonsils and an inflamed posterior pharynx. The lungs were clear. A diffuse precordial thrill was palpable over the heart and a harsh systolic apical murmur was heard. The clinical course was progressively downward and death occurred on October 4. The blood counts during the course of treatment are included in Table 1.

Drug therapy prior to hospitalization included tetanus antitoxin, wet dressings of chloramine, ferrous sulfate and sulfathiazole

myocardium and stomach. The right lung contained numerous small abscesses. The softened liver extended 7 cm. below the costal margin in the mid-clavicular line and showed toxic central necrosis. Two areas of ulceration, each 2.5 cm. in diameter, were found in the terminal ileum which contained blood in the lumen. Grossly the kidneys were enlarged and showed hemorrhage in the pelvis.

Anatomic Diagnoses: Aplastic anemia; terminal septicemia; multiple abscesses of right lung; toxic central necrosis of liver;

petechial hemorrhages of pleura, myocardium and stomach; ulceration of ileum; parenchymatous degeneration of kidneys; abscess of right buttock; aplasia of bone marrow.

Microscopic examination of heart showed edema and advanced parenchymatous degeneration. Passive congestion and emphysema were observed in the *lungs*. The *liver* showed fatty infiltration, serous hepatitis and toxic central necrosis. Marked parenchymatous degeneration of *kidneys* was present.

The *bone marrow*, which showed little hematopoietic tissue, consisted of loose interlacing threads of the walls of sinusoids containing an occasional nucleus. The nucleated blood cells which remained were mainly normoblasts and none of the myelogenous series could be recognized. A few large cells with vacuolated pink cytoplasm which may have been late megalocytes were seen. An occasional closed sinus was dilated with erythrocytes and rarely with developing late normoblasts.

CASE 2. L. B., a 9½ year old white male, was admitted to this hospital the third time on Oct. 15, 1943, with a history of bruising for 6 weeks and vomiting blood. The child's first admission from May 5 to 12, 1941, was for the repair of a right indirect inguinal hernia and undescended testicle. The second admission from March 28 to April 5, 1942, was because of an acute bronchopneumonia. In the interim between the second and third admission, on Oct. 15, 1943, the child received 28 gm. of sulfathiazole and had a sulfathiazole bandage applied to the right leg for 4 days.

On the later date the child appeared acutely ill with blood crusts around the external nares and large ecchymoses on all extremities. The temperature was 100° F. and the pulse rate was 90 per minute. The anterior cervical and axillary lymph nodes were discrete and palpable. The lungs were clear but a systolic atypical murmur was heard. Blood examinations are recorded in Table 1. The clinical diagnoses were acute granulocytopenia and purpura of undetermined origin. Death occurred on October 17. The known *drug therapy* included 34 gm. of sulfathiazole and the application of a sulfathiazole bandage.

At *autopsy* (6½ hours after death) the left pupil was considerably dilated and blood

crusts were present in the nares, mouth and right external auditory meatus. In the *skin* many ecchymoses were observed. The chest showed an enlarged *thymus*, petechial hemorrhages along the anterior coronary groove and extensive bronchopneumonia in both *lungs*, from which *Hemophilus influenzae* was cultured. The *liver* extended 4 cm. below the right costal margin and showed central toxic necrosis. Partially digested blood was present in the *stomach*, *ileum* and *colon*. The Peyer's patches and solitary lymph follicles were enlarged. *Bone marrow* from the rib appeared pale and reduced in amount. Direct smears were devoid of granulocytes and contained only a few erythrocytes.

Anatomic Diagnoses: Aplastic anemia; multiple ecchymoses of skin; tracheobronchitis (*H. influenzae*); bronchopneumonia; petechial hemorrhage of pericardium; massive hemorrhage into gastro-intestinal tract; toxic central necrosis of liver; parenchymatous degeneration of kidneys; Meckel's diverticulum; hypoplasia of bone marrow.

Microscopic examination showed irregularly distributed areas of bronchopneumonia. Chronic pericholangitis, serous hepatitis and toxic central necrosis were observed in the *liver*, and parenchymatous degeneration was present in the *kidneys*. The *bone marrow* consisted of a network of fine red lines which represented the walls of sinusoids. A few closed sinusoids showed developing cells, most of which were late normoblasts. No cells of the granulocytic series, very few erythrocytes and a rare megakaryocyte were observed.

CASE 3. A. T., a 3 year and 9 month old white male, was admitted to this hospital on Dec. 3, 1942. Three weeks previously the child had been in the Pittsburgh Municipal Hospital for 1 week with a tentative diagnosis of tonsillar diphtheria for which he received sulfanilamide (amount not obtainable) and 80,000 units of diphtheria antitoxin. Past medical history was negative. The child appeared pale and poorly nourished. A few small posterior cervical lymph nodes were palpable. The temperature was 103° F. and the pulse rate was 130 per minute. Physical examination revealed no abnormalities other than severe anemia with a questionable primary blood dyscrasia. On January 23 the gastric contents contained no free hydrochloric acid. The skull Roent-

gen ray showed no pathologic change. The blood counts are recorded in Table 1. Many transfusions of both plasma and whole blood increased the hemoglobin and red cell count but had little effect on the number of white cells, and just before death granulocytes completely disappeared from the circulation. A septicemia developed from multiple staphylococcal skin abscesses and death occurred on February 2.

Drug Therapy. An unknown amount of sulfanilamide and 80,000 units of diphtheria antitoxin were given in the Municipal Hospital. In our hospital pentnucleotides, yellow bone marrow and iron compounds were given for the anemia and sulfathiazole ointment was used for the skin abscesses.

At *autopsy* (1½ hours after death) widespread red maculopapules and pustules were present over the body. The tissues of the anterior *mediastinum* were infiltrated with fluid and both pleural cavities contained clear fluid. The *lungs* showed scattered areas of bronchopneumonia and a few small abscesses containing staphylococci and streptococci on the anterior surface. The *liver* extended 5 cm. below the costal margin and was dotted with small multiple abscesses which were also present in the kidneys and spleen. The *stomach* contained 50 cc. of coffee-ground mucoid fluid.

Anatomic Diagnoses: Aplastic anemia; bacteremia (staphylococcal); generalized embolic abscesses of lung, liver, kidney and spleen; bronchopneumonia (*H. influenzae*); parenchymatous degeneration of kidneys; aplasia of bone marrow.

Microscopically both lungs contained patches of bronchopneumonia and multiple abscesses which consisted of necrotic tissue devoid of granulocytes. The *spleen*, *liver* and *kidneys*, likewise, showed many embolic agranulocytic abscesses. Serous hepatitis was also present in the liver. The *bone marrow* was hypoplastic and contained several small abscesses made up of clumps of staphylococci, almost no polys, and a dense peripheral zone of degenerating erythrocytes and nucleated red blood cells. The open sinuses were dilated with serum containing an occasional red cell and their walls appeared as thin red lines with an occasional nucleus. The closed sinuses formed a network of red staining threads, many of which were of double contour. Occasionally these were separated and distended with from 12

to 20 erythrocytes and a rare nucleated red cell. The walls showed an occasional developing erythrocyte. Practically no cells of the myelogenous series were recognized and only a rare megakaryocyte was noted.

CASE 4.—D. L., a 4½ month old emaciated white male was admitted to this hospital on Jan. 8, 1945, because of pallor and weight loss. The child, a 7 month baby at birth, was well until 1 month before admission when he developed a dry cough. On Dec. 23, 1944, iron was prescribed at home but he vomited frequently thereafter and lost weight. Several small shotty anterior cervical and axillary lymph nodes were felt. Over the base of the left lung there was decreased resonance. The heart was normal except for some tachycardia. The liver extended to the level of the umbilicus and the spleen was palpable. Diagnostic impressions were a blood dyscrasia of unknown origin and pneumonia of the left lower lobe. The blood cell values are included in Table 1. The illness ran a rapid course and the child died on Jan. 9, 1945.

Drug Therapy. The only obtainable history of drug therapy was that of iron medication.

At *autopsy* (2½ hours after death) many small petechiae were noted over the surfaces of the *myocardium*, *lungs*, *liver* and *kidneys*. On section the lungs showed numerous patchy areas of bronchopneumonia. The liver had the mottled appearance of toxic central necrosis. Hemorrhage was present in the medulla of both *adrenals*. Smears from the *bone marrow* revealed a few erythrocytes, some normoblasts with a bluish or gray cytoplasm and an occasional neutrophil.

Anatomic Diagnosis: Aplastic anemia; bronchopneumonia; petechial hemorrhages of lungs, liver, heart and kidneys; fatty infiltration of liver; toxic central necrosis of liver; hypertrophy of spleen and hypoplasia of bone marrow.

Microscopically the *lungs* showed an interstitial pneumonia, chronic passive congestion, atelectasis and emphysema. Besides fatty infiltration and granular degeneration of the *liver* there was a central and focal toxic necrosis. The areas of focal necrosis closely resembled those which have been described from this laboratory in sulfonamide poisoning.¹ These areas were irregular in size and distribution, and showed varying degrees of necrosis and degeneration of liver

cells. Frequently such degenerating cells contained neutrophils. The central necrosis involved one-third to one-half of the lobule in which many hepatic cells exhibited marked loss of cytoplasm or had completely disappeared. The *spleen* contained areas of focal toxic necrosis, especially beneath the capsule. The *liver* and *spleen* exhibited extramedullary hematopoiesis. The sinusoids of the *lymph nodes* were dilated and contained many large macrophages with a reddish cytoplasm, probably due to ingested red blood cells. Parenchymatous degeneration was marked in the *kidneys* where a few small areas of focal necrosis occurred in the cortex.

Sections of *bone marrow of rib* showed hypoplastic tissue in which the walls of the sinusoids stained as reddish interlacing threads with reduced cellular formation. Almost no granulocytic cells were present. Here and there an occasional eosinophil as well as a rare neutrophilic myelocyte was noted. No megakaryocytes were encountered.

CASE 5. J. M. R., a 6½ year old female, had 3 periods of hospitalization at this hospital, namely, July 7 to 12, July 28 to August 29 and November 23 to December 4, 1943. A diagnosis of rheumatic fever was made in March 1943. On July 7 a tonsillectomy was performed and the patient was discharged 5 days later. This operation was followed by an intermittent fever with chills which occasioned the second admission, during which time she received sulfadiazine. Repeated blood cultures were negative. Cultures of feces were also negative. Two weeks previous to the third admission the child developed pneumonia. At this time the cervical and inguinal lymph nodes were palpable. Breath sounds were diminished in the left base posteriorly and the heart was slightly enlarged. The pulse rate was rapid and there was an apical systolic murmur. Abdominal palpation was negative and the reflexes were physiologic. Urinalyses showed a faint trace of albumin. The blood counts are recorded in Table 1. Diagnostic impressions were rheumatic heart disease with mitral insufficiency and anemia with granulocytopenia. In spite of repeated transfusions and intensive anti-anemic therapy the illness ran a rapid course with gradual decrease in cellular blood elements. The patient died on December 4 with a

diagnosis of aplastic anemia. Permission for *autopsy* was not obtained.

Drug Therapy. During the second hospitalization period, the child received 14 gm. of sulfadiazine and 2.6 gm. of sulfanilamide. Following this therapy, 17 gm. of a sulfa drug were given at home. Other treatment included anti-anemic medication and salicylates.

CASE 6. A. Z., an 8 year old female, was admitted to this hospital on March 14, 1945, subsequent to 2 admissions to the Uniontown Hospital. During the first admission from July 31 to Sept. 11, 1944, the child received a sulfonamide drug for 2 days for a fever of unexplained origin. Repeated blood cultures and agglutination tests at that time were negative. The diagnoses were bilateral suppurative otitis media and aplastic anemia. On the second admission to the same hospital on Jan. 28, 1944, blood cultures were positive for hemolytic streptococcus. Roentgen ray pictures showed an irregular rarefaction of the left femur. The blood counts are tabulated in Table 1. On March 14, 1945, the patient was referred to this hospital. Physical examination revealed a pale, well-developed but poorly nourished child. Both ear drums were reddened. The mucous membranes were pale, the tonsils were hypertrophied, the pharynx was injected and the superficial lymph nodes were enlarged, discrete and non-tender. Examination of chest and abdomen were negative. Pain was elicited over both femurs and great toes on palpation. Blood transfusions and penicillin injections somewhat improved the blood picture (Table 1). A sternal marrow puncture on March 29 contained only mature red cells, lymphocytes and lymphoblasts although a few cells may have been questionable granulocytes. The blood picture suggested aplastic anemia. Repeated blood cultures were negative. During hospitalization, the temperature was septic in type and fluctuated between 98° and 107° F. The child ran a progressively downhill course and death occurred on April 7. Permission for autopsy was not obtained.

Drug Therapy. Prior to her first period of hospitalization this child was treated with a sulfonamide drug of which we could obtain neither the type nor the exact dosage. Following this therapy, she had 3 intensive courses of penicillin injections.

Discussion. As we have previously indicated, aplastic anemia, especially in children, is of rare occurrence. In this hospital during the past 16½ years a total of 7 cases including the 6 reported in this paper has been encountered. The first of these 7 cases occurred between the years 1928 and 1942, inclusive, and was classified as idiopathic, as no definite etiologic factor could be found. The remaining 6 cases occurred in the 2½ years ending July 1945, and from the available clinical and pathologic evidence their origin, except in 1 case (Case 4), can be attributed to the sulfonamides administered. In Case 4 the pathologic findings implicated sulfonamides. Although the incidence of aplastic anemia during the last 2½ years has been markedly increased, it should be noted that many of these patients were referred to this hospital from outside the Pittsburgh area. The biennium and a quarter in which these aplasias developed has been marked by an extensive clinical use of sulfadiazine and sulfathiazole which have largely superseded the earlier prescribed sulfanilamide and sulfapyridine. These latter drugs, so far as our records are concerned, gave a lower incidence of blood dyscrasias. The size of the dose is important and many of the patients developed pathologic changes in the blood following high dosage, *e. g.*, 27 gm. of sulfadiazine and 34 gm. of sulfathiazole. It is often difficult to obtain an accurate history of the amount of drug and the duration of its use. The age incidence among the 6 children has ranged from 4½ months to 13 years, and sex does not appear to be an important factor. In the 4 cases in which autopsy tissues were examined the deleterious effect of the drug was not limited to the bone marrow and lesions were also found in the liver and other organs. It is worthy of note that, although there was considerable accompanying liver damage, jaundice and renal manifestations rarely were observed with sulfadiazine as had been the case in this hospital previously with sulfapyridine. The bone marrow

sections of aplastic anemia indicated an almost complete loss of all hematopoietic cells and especially the primitive cells lining the sinusoids, which picture suggested that the deleterious effect of the drug occurs primarily in the endothelial lining of these channels.

The bone marrow of children is apparently much more labile and susceptible to the toxic action of the drug than that of adults; hemolytic rather than aplastic anemia has been more frequently recorded in grown individuals. Because this condition is frequently associated with preëxisting infection, particularly of the upper respiratory tract, it is believed that the bone marrow as well as other tissue may have been depleted of enzyme by bacterial toxins early and thus rendered more susceptible. The pathogenesis of the lesions resulting from the action of the drug may possibly be on the basis of an acquired hypersensitivity, although we are inclined to interpret them as a direct interference with the utilization of enzymes which are concerned in the development and maturation of the various cells of the bone marrow. The sensitivity theory has for its support the fact that repeated series of dosage are found in some of the cases. A basis for the second or direct tissue impairment theory lies in the fact that most of the patients have a history of previous or concomitant infection. Data considered in a later paper related to the treatment of the sulfonamide granulocytopenia would confirm the belief that the pathogenesis lies in the interference of enzymes necessary to the development of the marrow. This view brings up the question as to whether the sulfonamides have an equally injurious and inhibitory effect upon the anlage of the red blood cells, of the neutrophil and of the platelet, and at what point in each of the developing series the sulfonamide exerts its initial toxic action. The anlage of the neutrophil is apparently more susceptible than that of the other 2 series. Sections of bone marrow from patients with aplastic anemia and with granulocytopenia would indicate the point

of attack to be on the early and more primitive cells of the series. Further evidence of this belief is the observation that in the restitution of the maturation process by enzymic therapy there is little increase in the reticulocytes. As is known, the protoporphyrin which characterizes the reticulum of the red cell is incorporated in the early stages of the developing cells, and persists only in cells whose maturation has been delayed, and which

are subsequently released into the circulation upon treatment.

Summary. In 4 of 6 described cases of aplastic anemia associated with sulfonamide therapy, bone marrow sections taken at autopsy revealed an extensive hypoplasia. The depletion of hematopoietic tissue is interpreted as resulting from direct injurious action of the drug on the early developing cells of the marrow.

REFERENCES

1. MENTEN, M. L., and ANDERSCH, M. A.: *Ann. Int. Med.*, **19**, 609, 1943.
2. MEYER, L., and PERLMUTTER, M.: *J. Am. Med. Assn.*, **119**, 558, 1942.
3. STRAUSS, A. M.: *J. Clin. Path.*, **13**, 249, 1943.
4. SUTLIFF, W. D., HELPERN, M., GRIFFITH, G., and BROWN, H.: *J. Am. Med. Assn.*, **121**, 307, 1943.

BLOOD CHANGES RELATED TO SULFONAMIDE THERAPY

II. GRANULOCYTOPENIA ASSOCIATED WITH USE OF SULFONAMIDES

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IN the preceding paper, 6 cases of aplastic anemia occurring in patients in this hospital during the past $2\frac{1}{2}$ years were described. The fact that these aplasias were associated with sulfonamide therapy early suggested that a series of progressive granulocytopenias related to the use of these drugs might also be found. During the first 3 months of 1944 and 1945 the blood counts of patients were followed with particular reference to granulocytopenias developing during treatment with the sulfonamides. It was found that during 1944 there was a high incidence of neutropenias and that in the following year, when penicillin treatment had replaced much of the sulfonamide therapy, this incidence had been reduced almost one-half. The blood counts which each patient receives in the hospital have for many years been made and tabulated daily by 2 members of the laboratory staff, thus it was possible to make a comparison of the number of granulocytopenias studied in 1944 and 1945 with those listed from 1936 to 1943 inclusive. This comparison revealed that previous to the introduction of sulfonamide medication into the hospital wards in 1940, the incidence of granulocytopenias averaged 3% of the number of admissions and in the years following there was a gradual increase which reached a maximum of 12% in 1944 when the use of sulfadiazine was at its peak. The varying incidence of granulocytopenias in relation to the sulfonamides is discussed in the following pages.

Reports in the Literature. Coincidental with the clinical use of these drugs, reports have been published of their toxic effects, among which latter are a moderate number of granulocytopenias. The first mention of leukopenia associated with sulfonamide therapy, which we have found, is that by Young,²¹ who in 1937 described this condition developing in a patient following the use of sulfanilamide. In 1938, Lloyd, Erskine and Johnson¹⁹ noted 4 cases of moderate granulocytopenia in 36 adults treated with sulfapyridine. In 7 children given this drug for gonococcal infections, 1 child developed a mild granulocytopenia. Kracke¹⁸ has collected 6 other references for 1937 in which agranulocytosis followed the administration of sulfanilamide. In 1939, Morgan and Detweiler²³ treated 76 patients suffering from pneumonia with sulfapyridine and observed leukopenia in 8 individuals, 1 of whom died. In 1941, Rinkoff and Spring²⁵ reported 6 cases, with 2 deaths, illustrating myeloid depression occasioned by sulfanilamide and sulfapyridine. Kennedy and Finland¹⁶ described an agranulocytosis in a patient with endocarditis treated with sulfathiazole, and these authors⁸ also reported a fall in the leukocyte count below 4000 cells per c.mm. in 9 out of 146 persons treated with sulfadiazine. Long, Haviland, Edwards and Bliss²⁰ found 0.4% leukopenias in 1000 patients receiving sulfanilamide, 0.9% among 297 patients receiving sulfapyridine and 1.6% among 271 patients receiving sulfathiazole. Flippin, Rose, Schwartz and Domm¹¹ listed a total of 2% leukopenias with sulfadiazine, as compared with 3% following sulfathiazole in 200 treated patients. Finland, Peterson and Goodwin⁹ found 3 granulocytopenias below 4000 per c.mm. among 460 patients receiving either sulfadiazine or sulfathiazole. Sutliff and

associates,²⁹ investigating sulfonamide intoxication as a cause of death in New York City in 1941, recorded 8 cases of agranulocytosis among 28 deaths following the use of various sulfonamide compounds. Hall and Spink¹³ treated 116 patients with sulfamerazine and noted 1 case of leukopenia. In a survey of hematology for 1943, Bethell, Sturgis, Mallery and Rundles⁴ collected 19 published cases of agranulocytosis due to various sulfonamide compounds. In a study of the results of the treatment of 186 patients with different sulfonamides, Frist¹² described 3 cases of agranulocytosis with 2 deaths. Vilter and Blankenhorn³⁰ analyzed 116 toxic reactions, including 2 cases of agranulocytosis resulting from the use of the newer sulfonamides, on 1936 patients during the 4 years ending with 1944. In a study of 1357 patients, Plummer and Wheeler²⁵ found 15 cases of granulocytopenia. Various authors have reported single cases of leukopenia with different sulfonamide compounds and a few of these are appended. An unusual case of fatal agranulocytosis following intraperitoneal implantation of 5 gm. of sulfanilamide was described by Arrowsmith, Binkley and Moore.¹ Favorite, Reiner and London⁷ reported a case of leukopenia due to sulfamerazine and Sutherland²⁸ 1 due to sulfanilamide. Park,²⁴ Blue,⁵ and Koteen¹⁷ each described a case following sulfadiazine, and Baker and Fenner² observed another case following sulfapyridine.

Only a few publications on retrograde changes occurring in the blood of children treated with sulfonamides have appeared. The report of Lloyd *et al.*¹⁹ has already been cited. Barlow³ observed agranulocytosis 7 days after the ingestion of 1.25 gm. of sulfapyridine in an infant 1 year and 7 months old, and Kato and associates¹⁵ noted a case of fatal agranulocytosis after sulfathiazole treatment in an infant 8 weeks old. Three cases of agranulocytosis following sulfapyridine, 2 of which were fatal, were described by Rosenthal and Vogel.²⁷ Herlitz¹⁴ recorded a 4% incidence of granulocytopenia following the use of sulfathiazole and showed that in 3 children there was an accompanying myeloid depletion of the bone marrow. Fischer and Agerty,¹⁰ in 2 papers, stated they found no marked change in the blood of children treated for pneumonia with sulfapyridine and sulfathiazole. On the other hand, Dowrie and Abramson⁶ found

24 cases of granulocytopenia in 54 sulfadiazine treated children (44%) and 20 cases in 53 sulfathiazole treated children (38%).

Results and Discussion. A cursory survey of the daily counts with the patient's name listed during 1942 and 1943 in this hospital indicated that the incidence of granulocytopenias was highest in the first 3 months of the year, during which period upper respiratory infections were most frequent. The blood counts as they were recorded daily during each first quarter of the years 1944 and 1945 were, therefore, chosen for a study of the frequency of blood changes referable to retrograde myeloid changes associated with sulfonamide therapy. Our series includes the granulocytopenias of 3000 or less granular cells per c.mm. developing in children during these 2 periods. Patients suffering from pertussis, leukemia and conditions definitely unrelated to sulfonamide therapy were excluded. Special effort was made to secure complete histories, especially of previous medication, and considerable difficulty was frequently encountered in obtaining information concerning sulfonamide therapy before admission of the patient to this hospital. For the past 4 years the morphologic blood work has been under the direct supervision of one of us (E. G.), who has made most of the differential counts.

The data collected during 1944 and 1945 are epitomized in the latter parts of Tables 1 and 2. The 125 instances of low leukocyte counts tabulated from Jan. 1 to April 1, 1944, occurred among 1021 admissions, that is, 12% of the total number of patients. The 79 instances of low leukocyte counts found during the same period in 1945 occurred among 1039 admissions, or 7.6% of the total number of patients.

In 1944, approximately 650 patients received sulfonamides, of which number 125 (19%) developed neutropenia. In 1945, approximately 360 patients received sulfonamides and of this number 79 (21%) developed neutropenia. By actual statistical count the 125 granulocytopenias in

1944 fell to 79 in 1945, although the total number of patients admitted to the hospital in these 2 years was practically the same. This reduction of 40% was due to partial replacement of sulfonamide therapy in the latter year by penicillin. In contrast, however, the percentage of myeloid depressions due to administered sulfonamides in each of these 2 years remained practically the same. The percentage of granulocytopenias in this biennial period were equal, affecting about 20% of all children receiving the drug.

The fact that the total number of children developing agranulocytosis in 1945 was about half as great as that in the previous year requires some comment. Several factors may have been responsible. First, as already noted, in 1945 many patients received penicillin in place of the sulfonamides and it has been our experience that little or no depression of hematopoietic activity is caused by penicillin, a fact noted by other workers. Secondly, there was some change in the type of upper respiratory infections in the latter year. In 1945, there was a predominance of influenzal tracheitis, fewer typical childhood pneumonias and a moderate number of atypical pneumonias. Furthermore, the duration of treatment of many children with the sulfonamides was limited to 2 or 3 days, and often then replaced by penicillin. A considerable number of milder leukopenias with a count slightly higher than 3000 cells per c.mm. occurred but these are not included because they lie in the range of physiologic variations. The percentages obtained by us for neutropenias developing with the use of sulfonamides are of lower value than the incidence of 38% and 44% found by Dowrie and Abramson,⁶ but these authors studied a more or less selected group of patients and our series represents consecutive unselected cases. Repeated blood examinations made on many of the leukopenic children who at our request were brought back to the dispensary 2 weeks after their discharge for a check-up blood count disclosed that

the blood of a number had acquired a normal complement of cells during that time. In 22 patients in the 1944 series, whose white blood cell count did not become normal within 2 weeks after discontinuance of the drug, examinations were repeated 6 and 9 months later, and 10 of the 22 continued to have granulocyte counts of 3000 or less per c.mm., and 5 others had granulocyte counts between 3000 and 4000 per c.mm. The total number of the persisting granulocytopenias could not be accurately determined but the above observation would seem to indicate a significant number of children treated with sulfonamides, about 40%, had acquired a more or less permanent disturbance of the myelogenous mechanism. This finding confirms our conviction previously stated,²¹ that repeated courses of sulfonamide medication tend to establish a lower pharmacologic resistance possibly the basis of what has been designated "drug sensitivity."

Having established by detailed study of consecutive individual cases the number of neutropenias developing in 1944 and 1945, we were interested in ascertaining by compilations made from blood counts listed in files of earlier years the number of similar granulocytopenias occurring previously. The data obtained for the 5 years ending in 1940 previous to the general use of the drug, through the years 1940 with small amounts and 1941 with a moderate supply of sulfapyridine, as well as for 1942 and 1943 with an increasing usage of sulfadiazine are included in Table 1. It should be mentioned that a limited amount of sulfapyridine was used during 1938 and 1939 in a study²² of the effects of this drug on childhood pneumonia. In the 5 years preceding the introduction of sulfonamide medication the number of neutropenias per year averaged about 3% (Table 1). We could not determine the cause of the high percentage in 1937 and the low percentage in the succeeding year. In 1941 and 1942 the first biennium in which sulfapyridine was used, but in relatively moderate

TABLE 1.—FREQUENCY OF GRANULOCYTOPENIA DEVELOPING DURING JANUARY, FEBRUARY AND MARCH 1936 TO 1945 INCLUSIVE

	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945
Patients admitted to hospital	494	684	768	765	812	797	958	1003	1021	1039
Patients developing granulocytopenia	20	31	7	26	41	62	67	104	125	79
% of granulocytopenias	4.0	4.5	0.9	2.9	3.8	7.7	7.0	10.3	12.0	7.6

TABLE 2.—AGE INCIDENCE OF DIFFERENT GRADES OF GRANULOCYTOPENIAS OCCURRING FROM 1931 TO 1945 INCLUSIVE

Age										
	3 mos. or less	3 to 6 mos	6 to 9 mos.	9 to 12 mos.	12 to 18 mos.	18 to 24 mos.	2 to 4 yrs.	4 to 6 yrs.	6 to 12 yrs.	Total
1936:										
I										
II										
III	1	1	1	3
IV	1	4	1	1	1	..	8	..	1	17
1937:										
I										
II	1	1
III	1	2	3	1	1	1	1	1	2	13
IV	1	3	2	1	5	1	2	1	1	17
1938:										
I										
II										
III	1	1
IV	3	3	6
1939:										
I										
II										
III	..	2	1	3
IV	4	5	4	1	1	1	2	2	3	23
1940:										
I										
II										
III	2	2	2	..	2	..	5	13
IV	4	4	1	..	2	2	6	6	3	28
1941:										
I										
II	..	1	1	2
III	1	3	2	2	4	1	1	3	2	19
IV	3	3	7	3	9	5	4	3	4	41
1942:										
I	..	1	1	2
II	1	1
III	1	2	2	5	3	..	3	1	3	20
IV	4	8	6	2	2	7	7	2	6	44
1943:										
I	2	2
II	2	..	1	..	1	1	..	5
III	4	6	6	1	8	3	8	2	3	41
IV	3	11	4	5	12	3	11	1	6	56
1944:										
I	2	2
II	..	1	1	..	2	..	1	1	..	6
III	..	2	3	1	7	3	15	9	10	50
IV	1	4	4	2	6	6	20	9	15	67
1945:										
I										
II			3	1	1	5
III	2	2	1	7	4	..	9	2	3	30
IV	4	2	2	5	12	3	6	2	8	44

I, white cell count containing less than 500 granulocytes per c.mm.
 II, white cell count containing between 500 and 999 granulocytes per c.mm.
 III, white cell count containing between 1000 and 1999 granulocytes per c.mm.
 IV, white cell count containing between 2000 and 3000 granulocytes per c.mm.

amount, the number of leukopenias rose to more than double this figure. In the biennium of 1943 and 1944 the clinical use of sulfadiazine reached a maximum with smaller amounts of sulfathiazole being prescribed. The rising incidence of the leukopenias from 1941 to 1944 inclusive undoubtedly paralleled the augmented use of the drug.

Furthermore, with the greater clinical use of the drug, there appeared for the first time in 1941 neutropenias below 1000 cells per c.mm. (Table 2) and in the following 3 years, as the cases with prescribed drug multiplied, neutropenias below a count of 500 per c.mm. were encountered. This latter group of exaggerated neutropenias was absent in 1945, as the sulfonamides were gradually superseded by penicillin. Age distribution as displayed in Table 2 apparently signifies that age *per se* is not a factor influencing frequency.

A survey of the hemoglobin and red blood cell counts of children, whose blood exhibited granulocytopenia, did not usually reveal an accompanying anemia. When a fall in the red blood cell counts was manifest, it occurred later in treatment than the neutropenia, and was of less intensity. In a few patients on whom platelet counts were made concomitantly these elements appeared, likewise, to be more resistant than the granulocytes to the deleterious action of the sulfonamide. Sternal punctures, as well as bone marrow, obtained at autopsy in a few patients showing neutropenia but dying from other causes, also indicated that the susceptibility of the early myeloid elements to the toxic action of the sulfonamides is

greater than that of the precursors of the red blood cell and platelet. The relative frequency of low granulocyte counts in children would denote a greater instability of bone marrow in relation to sulfonamides in young individuals than in adults.

Because, in the cases studied in 1944 and 1945 the relative quantities of the 4 types drug used, namely, sulfanilamide, sulfapyridine, sulfadiazine and sulfathiazole, could not be accurately determined, it has not been possible to decide whether there is any appreciable difference in the extent of their individual injurious action on bone marrow. The reduced conjugation *in vivo* and the related more prolonged maintenance of high blood level of the 2 latter mentioned preparations, in contrast to the first 2, may be a significant factor in the increased incidence of granulocytopenias reported here.

Summary. In an analysis of the granulocytopenias with less than 3000 cells per c.mm. occurring in the first quarter of the years from 1936 to 1945 inclusive, an average frequency of 3% of the number of admissions found before the use of the sulfonamides was followed by a gradually increasing incidence which paralleled the augmented use of the drug. The incidence reached a maximum of 12% in 1944 when sulfadiazine medication was at its peak and diminished to 7.6% in 1945 when penicillin replaced much of the sulfadiazine. The percentage of neutropenias developing from sulfonamides in these 2 years, however, remained the same, namely, about 20% of all patients receiving the drug.

REFERENCES

1. ARROWSMITH, W. R., BINKLEY, B., and MOORE, C. V.: Ann. Int. Med., 21, 323, 1944.
2. BAKER, B. A., and FENNER, F.: Bull. War Med., 4, 166, 1943.
3. BARLOW, C. H.: Brit. Med. J., 1, 669, 1941.
4. BETHELL, F. H., STURGIS, C. C., MALLERY, O. T., and RUNDLES, R. W.: Arch. Int. Med., 74, 131, 1944.
5. BLUE, J. A.: AM. J. MED. SCI., 207, 453, 1944.
6. DOWRIE, J. O., and ABRAMSON, M. H.: J. Pediat., 24, 176, 1944.
7. FAVORITE, G. O., REINER, L., and LONDON, R.: J. Lab. and Clin. Med., 29, 899, 1944.
8. FINLAND, M., STRAUSS, E., and PETERSON, O. L.: J. Am. Med. Assn., 116, 2641, 1941.
9. FINLAND, M., PETERSON, O. L., and GOODWIN, R. A.: Ann. Int. Med., 17, 920, 1942.
10. FISCHER, C. C., and AGERTY, H. A.: Arch. Pediat., 58, 97, 1941.
11. FLIPPIN, H. E., ROSE, S. B., SCHWARTZ, L., and DOMM, A. H.: AM. J. MED. SCI., 201, 585, 1941.

12. FRIST, T. F.: War Med., 5, 150, 1944.
13. HALL, W. H., and SPINK, W. W.: J. Am. Med. Assn., 123, 125, 1943.
14. HERLITZ, C. W.: Acta Paediat., 29, 1, 1941.
15. KATO, K., SHERMAN, M. S., and CANNON, P. R.: J. Pediat., 22, 432, 1943.
16. KENNEDY, P. C., and FINLAND, M.: J. Am. Med. Assn., 116, 295, 1941.
17. KOTEEN, P.: J. Am. Med. Assn., 126, 833, 1944.
18. KRACKE, R. R.: J. Am. Med. Assn., 111, 1255, 1938.
19. LLOYD, V. E., ERSKINE, D., and JOHNSON, A. G.: Lancet, 1, 1305, 1938.
20. LONG, P. H., HAVILAND, J. W., EDWARDS, L. B., and BLISS, E. A.: J. Am. Med. Assn., 115, 365, 1940.
21. MENTEN, M. L., and ANDERSCH, M. A.: Ann. Int. Med., 19, 609, 1943.
22. MENTEN, M. L., MACDONALD, R. R., and BRÖNYKOVSKY, N.: Am. J. Dis. Child., 59, 497, 1940.
23. MORGAN, J. R., and DETWEILER, H. H.: J. Lab. and Clin. Med., 25, 275, 1939.
24. PARK, G. G.: Lancet, 1, 13, 1944.
25. PLUMMER, N., and WHEELER, C.: Am. J. Med. Sci., 207, 175, 1944.
26. RINKOFF, S. S., and SPRING, M.: Ann. Int. Med., 15, 89, 1941.
27. ROSENTHAL, N., and VOGEL, P.: J. Am. Med. Assn., 113, 584, 1939.
28. SUTHERLAND, M. E.: Lancet, 1, 1208, 1939.
29. SUTLIFF, W. D., HELPERN, M., GRIFFITH, G., and BROWN, H.: J. Am. Med. Assn., 121, 307, 1943.
30. VILTER, C. F., and BLANKENHORN, M. A.: J. Am. Med. Assn., 126, 691, 1944.
31. YOUNG, C. J.: Brit. Med. J., 2, 105, 1937.

BLOOD CHANGES RELATED TO SULFONAMIDE THERAPY

III. TREATMENT OF GRANULOCYTOPENIA WITH FOLIC ACID AND PYRIDOXINE HYDROCHLORIDE

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THE deleterious effects of sulfonamide compounds on the hematopoietic tissues of certain susceptible individuals has stimulated an interest not only in the elucidation of the factors concerned in the pathogenesis of the retrograde processes, but also in possible means of counteracting or correcting the bone marrow damage. Granulocytopenia and aplasia of bone marrow have in the past 4 years been produced experimentally in laboratory animals by the addition of known amounts of various sulfonamides to purified rations. In 1942, Daft, Ashburn and Sebrell,⁵ and Daft, Ashburn, Spicer and Sebrell^{6,27} recorded the occurrence of granulocytopenia and anemia in white rats when sulfaguandine and succinylsulfathiazole were fed with controlled diets, and in the following year Axelrod, Gross, Bosse and Swingle,¹ and Daft and Sebrell⁷ reported similar results. Kornberg, Daft and Sebrell¹⁹ repeated these experiments with sulfadiazine and sulfathiazole. The blood changes found in the sulfonamide treated rats were comparable to those observed by Wilson, Doan, Saslaw and Schwab,³¹ and Waisman and Elvehjem³⁰ in monkeys and by Campbell and associates² in chicks when these animals were fed with controlled diets, deficient in a factor which could be chemically separated from liver, yeast and spinach and with a widespread distribution such as in meat, soy bean, grass, oats and many other substances including bone

marrow. This factor has been variously designated vitamin B₁₂,¹⁵ folic acid,²¹ *Lactobacillus casei* factor,^{25,28} norite eluate factor^{16,17} and *Streptococcus lactis* R factor,²¹ depending upon the source, preparation and method of assay. The vitamin M of Day and his co-workers^{8,9,10,11,20} is another designation for an identical substance.¹² The restoration of normal blood values in the 2 groups of experimental animals, namely, sulfonamide treated and "folic acid" deficient, by administration of concentrated liver fractions or norite eluate of liver extracts, both of which apparently owed their activity to the presence of "folic acid," strongly implicated this enzyme as a basic factor in the underlying pathologic change of the bone marrow. Wright and Welch³² suggested that succinylsulfathiazole owes its injurious effects to a specific inhibitory action on certain enzyme systems, and Elvehjem¹³ in 1943 hypothesized that the blood dyscrasias arising in sulfonamide treated patients might be due to an interference with "folic acid" metabolism by the drug. Sharp *et al.*²⁴ tested such a hypothesis by the use of vitamin B₁₂ in 5 patients with anemia but obtained only a slight response.

In April 1944 we had the opportunity of trying a liver powder* containing 34 micrograms of *L. casei* factor per gm. for its effect in alleviating the neutropenia developing in children following the ingestion of sulfonamide. This powder was

* This liver powder and the preparations of *L. casei* factor were kindly supplied by Dr. T. H. Jukes of Lederle Laboratories, Inc., Pearl River, New York.

somewhat bulky and occasionally produced abdominal cramps in children when it was given to them in large amounts. The efficacy of this preparation in restoring blood counts to normal was tested on several patients in the Children's Hospital of Pittsburgh suffering from granulocytopenia following sulfonamide therapy, and also on a young woman who had aplastic anemia due to the sulfadiazine. Treatment gave no beneficial response in the latter person, and only slight temporary improvement in the blood count of the children. Early in 1945 we were supplied with a more purified liver concentrate in capsules, each of which contained 40 micrograms of *L. casei* factor. The dosage prescribed was 1 capsule 3 times a day regardless of the age of the patient. Infants and young children who could not swallow the capsule were given the contents in milk or other fluids. This concentrate produced little change in the leukocyte counts of 2 children after administration for more than 2 weeks.

In April 1945, we were supplied with a second lot of liver concentrate in capsules, each of which contained 48 micrograms of *L. casei* factor. The negative results obtained with the first sample of *L. casei* factor made us feel that possibly a second factor or enzyme might be involved in the development of the blood dyscrasias associated with sulfonamides. The conclusion of Hill, Norris and Heuser¹⁴ from experiments on chicks that another factor besides folic acid was necessary for the prevention of anemia produced by purified diet was supported by the finding of Scott *et al.*,²² that *L. casei* factor and a lactone derived from pyridoxine were required to prevent anemia developing in these birds fed on insufficient rations. Scott, Norris, Heuser and Bruce²³ showed that either one of the two lactones of pyridoxine, designated α pyracin and β pyracin, in combination of *L. casei* factor was more effective in preventing anemia in chicks than any one of the three substances used alone. Although a considerable literature on possible deficiency factors con-

cerned with anemia has accumulated, only a few references related to deficiency neutropenias are available. Intravenous injections of pyridoxine were credited with creating an increase in the granulocytic series, as well as improving the anemia, by Vilter, Schiro and Spies²⁹ in 2 patients with pernicious anemia, whose blood also showed a neutropenia. Cartwright and associates⁴ described a terminal leukopenia in 2 pigs fed on casein hydrolysate plus additions of vitamins and lacking pyridoxine hydrochloride but did not ascribe much significance to its occurrence. Cantor and Scott³ obtained good clinical results in a case of sulfathiazole neutropenia by the intravenous daily injections of 125 to 200 mg. of pyridoxine for 6 days, a finding which induced us to supplement the *L. casei* factor with this medicament. Pyridoxine hydrochloride in amounts of 50 mg., 3 times a day by mouth, was added to the daily prescribed *L. casei* factor. This report analyzes the results of treatment for neutropenia in 23 patients, including 22 children and 1 adult, a nurse. Nineteen patients have been given *L. casei* factor combined with pyridoxine and 4 patients *L. casei* factor alone. Of this number, 14 individuals have shown a considerable rise in the percentage of neutrophils (Table 1). The remaining 9 children, some of whom received inadequate dosage, responded less favorably (Table 2). The duration of the treatment which was from 3 days to 1 month has been determined largely by the speed of the neutrophil response and by length of time the patient remained in the hospital. Of the successfully treated patients, 2 require comment. The patient, L. K., No. 13, was hospitalized for a staphylococcic infection in the axilla and a cellulitis which had spread along the right arm. This infection was fairly persistent and the boy received a large amount of sulfadiazine together with penicillin for 3 weeks, when the leukocyte count fell suddenly. This patient was then treated in the hospital with penicillin together with the folic acid and pyridoxine for a couple of weeks, when the leukocyte

TABLE 1.—NEUTROPENIAS RESPONDING FAVORABLY TO L. CASEI FACTOR AND PYRIDOXINE HYDROCHLORIDE TREATMENT

Patient	Color	Sex	Age	Clinical diagnosis	Sulfonamide used	Duration of sulfonamide therapy, 1945	Amount of drug (gr.)	Penicillin (10 ³ units)	+ Roentgen ray, radium	Date of blood count	Hemoglobin (gm.)	RBC (10 ⁹)	WBC (10 ⁹)	Granulocytes (%)	Treatment	Duration of treatment
1. J. S.	W	M	4 mos.	Chronic bronchitis Enlarged thymus	D*	2-8 to 2-11	76	I: 2-12 II: 2-14 III: 2-26 IV: 8-20	11.2 11.2 12.0 10.5	3.80 3.80 4.20 3.80	12.4 10.6 8.0 10.6	23 23 60 40	Folic acid Pyridoxine	2 14 to 2 26 12 days
2. P. S.	W	F	4 mos.	Allergic dermatitis	†	II: 2-26 III: 3-19 IV: 7-20	10.2 11.0 11.8	3.65 3.50 3.90	12.4 9.4 11.2	18 54 45	Folic acid	2-9 to 2-24 5 days
3. P. M.	W	F	5 mos.	Nasopharyngitis	D	6-10 to 6-15	82	205	I: 5-30 II: 6-6 III: 6-19	10.0 13.0 12.8	3.55 4.40 4.15	11.2 10.3 14.2	45 23 54	Folic acid Pyridoxine	6-7 to 6-20 13 days
4. J. M.	W	M	6 mos.	Chronic sinusitis Rickets	D	6-23 to 6-24	34	210	I: 2-23 II: 3-3 III: 3-10	11.5 11.8 12.0	4.30 4.01 4.00	22.6 10.8 10.0	28 23 67	Folic acid Pyridoxine Brewer's yeast	3-7 to 3-10 3 days
5. C. L.	W	M	5 mos.	Bronchitis Pharyngitis Leukopenia	†	I: 3-4 II: 3-9 III: 3-30 IV: 8-3 V: 8-31	12.5 13.0 12.0 13.2	4.00 4.30 4.20 4.40	6.4 7.1 14.0 7.6 7.2	24 14 66 55 62	Folic acid Pyridoxine Brewer's yeast	3-9 to 3-17 8 days
6. D. S.	W	F	6 mos.	Bronchitis	D	2-13 to 2-26	173.2	360	II: 2-13 III: 3-19	10.2 11.0	3.65 3.50	7.0 9.4	19 54	Folic acid Pyridoxine	3-11 to 3-19 8 days
7. M. B.	W	F	8 mos.	Bronchitis Otitis media	D	2-25 to 2-26	20	I: 2-25 II: 2-28 III: 3-12 IV: 7-20 V: 8-22	10.0 11.0 11.8 10.8 11.5	3.40 3.75 4.00 3.70 3.70	4.5 7.4 10.4 8.1 8.8	24 19 55 40 55	Folic acid Pyridoxine Brewer's yeast	2-27 to 3-7 8 days

8. S. F.	W	F	11 mos.	Bronchitis Granulocytopenia	T†	†	250	II: 4-26 III: 5-11 IV: 7-24	11.0 11.0 11.7	3.80* 3.65 3.80	2.6 5.6 6.3	18 74 53	Folic acid Pyridoxine Brewer's yeast	4-28 to 5-13 15 days
9. T. R.	W	M	16 mos.	Bronchopneumonia Otitis media	D T	2-6 2-7 to 2-12	13	I: 2-6 II: 2-16 III: 2-20 IV: 7-27 V: 8-9	13.0 11.8 13.0 11.3 12.2	4.35 4.20 4.30 11.3 ..	13.8 8.2 16.2 11.3 9.9	60 27 68 67 44	Folic acid	2-17 to 2-20 3 days
10. C. J.	B	M	20 mos.	Bronchopneumonia	D	6-9 to 6-14	I: 6-9 II: 6-13 III: 6-19	11.0 11.0 10.5	3.75 3.65 3.60	16.5 4.5 8.6	78 29 60	Folic acid Pyridoxine	6-15 to 6-21 6 days
11. D. B.	W	M	2 yrs.	Bronchopneumonia	D	4-9 to 4-11	..	II: 4-9 III: 4-16 IV: 7-27	11.7 11.0 13.0	3.85 4.15 4.40	8.4 11.8 9.3	26 64 31	Folic acid Brewer's yeast Pyridoxine	4-10 to 4-15 5 days
12. C. E.	W	M	3 yrs.	Tracheobronchitis	D	1-24 to 1-26	II: 2-24 III: 3-14 IV: 8-29	10.5 12.0 11.5	3.45 3.95 3.76	4.2 7.0 9.2	15 63 57	Folic acid	7 days
13. L. K.	W	M	6 yrs.	Cellulitis, right arm and axilla	D	5-3 to 5-19	820	I: 5-3 II: 5-22 III: 6-21 IV: 7-21 V: 8-31	13.0 11.5 12.0 12.0 13.0	4.70 3.75 3.85 3.80 4.40	21.4 5.3 6.6 7.9 6.5	92 7 66 63 64	Folic acid Pyridoxine	5-21 to 6-21 31 days
14. E. P.	W	F	22 yrs.	Infectious hepatitis	D	6-6 to 6-7	48	I: 6-6 II: 6-8 III: 6-21	14.0 11.8 12.2	4.55 3.85 4.10	2.2 4.3 4.8	79 36 72	Folic acid Pyridoxine	6 18 to 6-30 12 days

* Sulfadiazine. † Type and amount of sulfonamide used not available. ‡ Amount of sulfonamide used not available.
I, Blood count before sulfonamide given in hospital. II, Blood count at peak of the granulocytopenia. III, Blood count after treatment with *L. casei* factor and pyridoxine.
IV, Blood count made later. V, Blood count made later. When I is omitted the leukocyte count which was identical was depressed when patient was admitted to hospital because of previous sulfonamide therapy.

TABLE 2.—NEUTROPENIAS LITTLE ALTERED BY L. CASEI FACTOR AND PYRIDOXINE HYDROCHLORIDE TREATMENT

Patient	Sex	Age (mos.)	Clinical diagnosis	Sulfonamide used	Duration of sulfonamide therapy, 1945	Amount of drug (gr.)	Penicillin (10 ³ unit)	Date of blood count	Hemoglobin (gm.)	RBC (10 ⁶)	WBC (10 ⁹)	Granulocytes (%)	Treatment	Duration of treatment
1. W. L.	W	M	1 ¹ Tracheobronchitis	D*	2-22 to 2-23	15.0	..	I: 2-23 II: 3-1 III: ..	12.2	3.95	8.8	27	Folic acid Pyridoxine Brewer's yeast	2-24 to 3-2 6 days
2. G. H.	B	M	2 Bronchopneumonia	D	4-8 to 4-10	34.0	..	I: 4-8 II: 4-11 III: 5-1	8.0 10.0 12.8	2.90 3.40 4.25	5.6 8.4 12.4	26	Folic acid Pyridoxine	4-12 to 5-1 18 days
3. C. H.	B	M	3 Bronchopneumonia	D	4-3 to 4-5	64.0	..	II: 4-3 III: 4-10	10.0 12.8	3.65 4.25	11.0 8.0	29 41	Folic acid Pyridoxine	4-4 to 4-10 6 days
4. C. F.	B	F	7 Bronchitis	D	3-14	39.0	..	II: 3-14 III: 3-22 IV: 7-20 V: 9-7	7.8 9.0 7.5	3.20 3.60 3.60	2.6 6.0 7.7	17 43 64°	Folic acid Pyridoxine Folic acid	3-16 to 3-22 6 days
5. G. S.	W	M	12 Pharyngitis Chronic tonsillitis	D	2-13 to 2-19	213.0	105	I: 2-12 II: 2-20 III: 3-20	10.2 9.5 12.0	3.45 3.20 3.85	10.0 7.0 9.0	43 36	Folic acid Pyridoxine	1-20 to 1-22 2 days
6. R. C.	W	M	14 Tracheobronchitis	D	3-25 to 3-28	55.5	..	I: 3-25 II: 3-28 III: 3-29	11.5 9.5 ..	3.75 3.62 ..	7.2 6.5 9.5	40 27 45	Folic acid Pyridoxine	2-30 to 4-1 2 days
7. J. K.	W	M	15 Tracheobronchitis	D	2-11	12.0	2455	I: 2-2 II: 2-28 III: 3-12	9.7 10.5 11.0	3.45 3.45 3.55	13.8 14.0 17.1	68 22 49	Folic acid Pyridoxine Brewer's yeast	3-2 to 3-12 10 days
8. K. Z.	W	F	18 Bronchopneumonia	D	1-15 to 1-16	78.0	..	I: 1-15 II: 1-25 III: 2-16	11.8 11.5 12.2	3.75 3.95 3.95	6.2 4.8 6.8	61 24 44	Folic acid Pyridoxine	1-29 to 2-10 11 days
9. L. L.	B	M	18 Bronchitis Tonsillitis	D	1-15 to 1-16	78.0	..	I: 1-15 II: 1-25 III: 2-16	11.8 11.5 12.2	3.75 3.95 3.95	6.2 4.8 6.8	61 24 44	Folic acid Pyridoxine	1-29 to 2-10 11 days

* Amount not available.

† Blood count before sulfonamide given in hospital.

I, Blood count made later.

II, Blood count made later.

III, Blood count made later.

IV, Blood count made later.

V, Blood count made later.

° After 2 weeks treatment with *L. casei* factor.III, Blood count after treatment with *L. casei* factor.

count returned to normal. The infection also cleared up. After 10 days at home the leukocyte count again fell below normal with a differential count of 50% granulocytes. He was given a second treatment at home for 2 weeks, at the end of which time the leukocyte count was fairly normal. A normal differential count has been maintained. The nurse, E. P., No. 14, had infectious hepatitis with jaundice, a condition which had been fairly frequent in this district among children. After a small dosage of sulfadiazine in the hospital, there was a further marked fall in the leukocyte count following which *L. casei* treatment was instituted. Treatment was discontinued when she returned to another hospital. Subsequently, a second affiliating nurse showed a similar neutropenia associated with infectious hepatitis but could not be treated for a sufficient period to assess the value of *L. casei* factor. Of the 11 patients who did not respond favorably, 3 children (G. S. No. 5, J. K. No. 7, and R. C. No. 6) received *L. casei* factor from 2 to 3 days only, a period of treatment too brief for lasting effect. The parents of these children, as soon as the temperature of the latter reached normal and the clinical condition appeared to be improved, insisted on taking them from the hospital. Two other children (C. H. No. 3 and C. F. No. 4), having received the drug for 6 days when they also were taken home, showed a moderate response in the leukocyte count, which might have reached normal if the treatment had been continued. There are 4 remaining patients (W. L. No. 1, G. H. No. 2, L. L. No. 9 and H. Z. No. 8) whose lowered counts were not much increased at the time of discontinuance of treatment. The first 2 of these were aged $1\frac{1}{2}$ and 2 months respectively, a period at which the bone marrow is relatively unstable. Furthermore, the concentrated liver is not well tolerated by infants and is frequently regurgitated or vomited. A persistent and intractable infection may have been responsible for

the prolonged neutropenia which failed to respond to treatment in H. K. No. 8.

One of the significant items revealed by both Tables 1 and 2 is that about half of the patients already had on entering the hospital a low neutrophil count, due, we believe, as the medical histories of many of the children indicated, to previous medication with 1 of the sulfonamides, usually sulfadiazine. The lack of repair of the initial damage to the hematopoietic tissue leaves the child with a damaged bone marrow inadequate to cope with subsequent dosage of the drug. This fact is shown in Table 1 by patients J. S. No. 1, P. M. No. 3, J. M. No. 4, and M. B. No. 7, and in Table 2 by W. L. No. 1, G. H. No. 2 and J. K. No. 7 who displayed further increase in neutropenia after relatively small amounts of sulfadiazine. Here is evidence of the deleterious effect of repeated courses of the drug therapy in children. Such residual damage probably delays the achievement of good results in treatment designed to restore bone marrow to normal.

Yeast was added to the diets of some of the children receiving the dual treatment in the hope that these organisms might convert the ingested pyridoxine to a more functional form because Snell²⁶ has shown that yeast can effect a conversion of this enzyme into the more active compounds, pyridoxal and pyridoxamine. Conversion compounds of pyridoxine are, according to Scott *et al.*,²² and Johnson, Hamilton and Mitchell¹⁸ more effective in preventing deficiency anemia in chicks than the original compound. Any beneficial effect due to the yeast, if it were present, was overshadowed by the intestinal gas and abdominal distention produced by the organisms. Substitution of yeast powder for the live yeast corrected much of the distention but did not materially improve the treatment as far as we could judge. Four unlisted children, whose ages varied between 1 and 4 years, having a neutropenia associated with hypothyroidism, were given *L. casei* factor and pyridoxine for varying periods of time without any

appreciable alteration in their white blood cell count. Another child 4 years of age with a neutropenia not related to sulfonamides, the cause of which we could not determine, likewise showed little beneficial effect from the treatment with the combined enzymes.

Subsequent blood examinations have been made on several of the treated patients in an attempt to evaluate the permanency of the restitution of the damaged bone marrow by the combined treatment.

For various reasons such tests could not be made on all of the patients studied. Nine children listed in Table 1 were brought back to the hospital by their parents for later blood counts. Although the later leukocyte counts obtained on children generally showed an improvement over the neutropenia occasioned by the sulfonamide, the variation exhibited by the granulocytic values would seem to indicate a persisting instability in the myeloid elements (Table 1 and 2, IV, V). The fact that L. K. No. 13, who received a total treatment for 30 days, has maintained a high white blood cell count suggests that either the arbitrarily chosen dosage of *L. casei* factor should be greater or the duration of the treatment increased. Leukocyte counts on patients listed in Table 2 showed little change in the leukocyte count following treatment. Varying grades of damage to the bone marrow may be produced by sulfonamides. These changes range from the mild degeneration reflected in slight depression of the neutrophilic count with spontaneous return to normal on discontinuance of the sulfonamide to the extreme destruction found in aplastic anemia as shown by severe neu-

tropenia and failure to respond to any known therapeutic agent. Obviously such variations call for widely differing periods of treatment to repair completely the damage.

It is possible that pyridoxine, the adjuvant selected by us for use with the *L. casei* factor, might advantageously be replaced by some other member of the vitamin B group. A few patients responded to *L. casei* factor alone. This observation suggests the possibility that this substance given in sufficient quantity might effect a satisfactory change in the leukopenia. At present we are testing the efficiency of a higher dosage of folic acid with a preparation kindly supplied us recently by Dr. T. H. Jukes.

Although the series of patients included in this preliminary report is not extensive and the results are less conclusive than might be desired, the results of the study are put on record in the hope that they may be of use to other workers in this field.

Summary. Of 22 children and 1 adult who had developed granulocytopenia, following sulfonamide therapy, 13 children showed a favorable response in the granulocyte count after treatment with *L. casei* factor. Pyridoxine hydrochloride was used as an adjuvant to *L. casei* factor in many of the children. White blood counts made on 9 of the 13 children at different periods of time after treatment indicated that the increase in granulocytes obtained with the *L. casei* factor was maintained in half of the children only. The low initial response as well as the subsequent variation in the level of granulocyte values is believed due to inadequate dosage of *L. casei* factor.

REFERENCES

1. AXELROD, A. E., GROSS, P., BOSSE, M. D., and SWINGLE, K. F.: J. Biol. Chem., 148, 721, 1943.
2. CAMPBELL, C. J., BROWN, R. A., and EMMETT, A. D.: J. Biol. Chem., 152, 483, 1944.
3. CANTOR, M. W., and SCOTT, J. W.: Science (L.S.), 100, 545, 1944; Canad. Med. J., 52, 368, 1945.
4. CARTWRIGHT, G. E., WINTROBE, M. M., BUSCHKE, W. H., FOLLIS, R. H., JR., SUKSTA, A., and HUMPHREYS, S.: J. Clin. Invest., 24, 268, 1945.
5. DAFT, F. S., ASHBURN, L. L., and SEBRELL, W. H.: Science, 96, 321, 1942.
6. DAFT, F. S., ASHBURN, L. L., SPICER, S. S., and SEBRELL, W. H.: Pub. Health Rep., 57, 217, 1942.
7. DAFT, F. S., and SEBRELL, W. H.: Pub. Health Rep., 58, 1542, 1943.
8. DAY, P. L., LANGSTON, W. C., and SHUKERS, C. F.: J. Nutr., 9, 637, 1935.

9. DAY, P. L., LANGSTON, W. C., and DARBY, W. J.: *Proc. Soc. Exp. Biol. and Med.*, **38**, 860, 1938.
10. DAY, P. L., DARBY, W. J., and LANGSTON, W. C.: *J. Nutr.*, **17**, 13, 1939.
11. DAY, P. L., LANGSTON, W. C., DARBY, W. J., WAHLIN, J. G., and MIMS, V.: *J. Exp. Med.*, **72**, 463, 1940.
12. DAY, P. L., MIMS, V., TROTTER, J. R., STOKSTAD, E. L. R., HUTCHINGS, B. L., and SLOANE, N. H.: *J. Biol. Chem.*, **157**, 423, 1945.
13. ELVEHJEM, C. A.: *Science (Suppl.)*, **97**, 12, 1943.
14. HILL, F. W., NORRIS, L. C., and HEUSER, G. F.: *J. Nutr.*, **28**, 175, 1944.
15. HOGAN, A. G., and PARROTT, E. M.: *J. Biol. Chem.*, **128** (Proc.), xlv, 1939; **132**, 507, 1940.
16. HUTCHINGS, B. L., BOHONOS, N., HEGSTED, D. M., ELVEHJEM, C. A., and PETERSON, W. H.: *J. Biol. Chem.*, **140**, 681, 1941.
17. HUTCHINGS, B. L., BOHONOS, N., and PETERSON, W. H.: *J. Biol. Chem.*, **141**, 521, 1941.
18. JOHNSON, B. C., HAMILTON, T. S., and MITCHELL, H. H.: *J. Biol. Chem.*, **158**, 619, 1945.
19. KORNBERG, A., DAFT, F. S., and SEBRELL, W. H.: *Science*, **98**, 20, 1943.
20. LANGSTON, W. C., DARBY, W. J., SHUKERS, C. F., and DAY, P. L.: *J. Exp. Med.*, **68**, 923, 1938.
21. MITCHELL, H. K., SNELL, E. E., and WILLIAMS, R. J.: *J. Am. Chem. Soc.*, **63**, 2284, 1941.
22. SCOTT, M. L., NORRIS, L. C., HEUSER, G. F., BRUCE, W. F., COOVER, H. W., JR., BELLAMY, W. D., and GUNSALUS, J. C.: *J. Biol. Chem.*, **154**, 713, 1944.
23. SCOTT, M. L., NORRIS, L. C., HEUSER, G. F., and BRUCE, W. F.: *J. Biol. Chem.*, **158**, 291, 1945.
24. SHARP, E. A., VONDER HEIDE, E. C., and WOLTER, J. G.: *J. Am. Med. Assn.*, **124**, 734, 1944.
25. SNELL, E. E., and PETERSON, W. H.: *J. Bact.*, **39**, 273, 1940.
26. SNELL, E. E.: *J. Biol. Chem.*, **154**, 314, 1944.
27. SPICER, S. S., DAFT, F. S., SEBRELL, W. H., and ASHBURN, L. L.: *Pub. Health Rep.*, **57**, 1559, 1942.
28. STOKSTAD, E. L. R.: *J. Biol. Chem.*, **139**, 475, 1941.
29. VILTER, R. W., SCHIRO, H. S., and SPIES, L. D.: *Nature*, **145**, 388, 1940.
30. WAISMAN, H. A., and ELVEHJEM, C. A.: *J. Nutr.*, **26**, 361, 1943.
31. WILSON, H. E., DOAN, C. A., SASLAW, S., and SCHWAB, J. L.: *Proc. Soc. Exp. Biol. and Med.*, **50**, 341, 1942.
32. WRIGHT, L. D., and WELCH, A. D.: *J. Nutr.*, **27**, 55, 1944.

VARIATIONS IN SUSCEPTIBILITY TO THERAPEUTIC MALARIA

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INDIVIDUALS show a variable response in their susceptibility to therapeutic malaria. During the past year 300 members of the Army (225 whites, 75 Negroes) with various types of neurosyphilis have been treated with therapeutic malaria at this hospital. These men represent a cross-section of the population of this country. Many of them have lived or served in areas where malaria is endemic.

Of the white patients, 208 were inoculated with *Plasmodium vivax*. Of these, 185 (90%) had a satisfactory therapeutic course of 10 or more paroxysms following the primary inoculation. Of the 23 patients who failed to get an adequate febrile reaction with *P. vivax*, 14 gave a history suggestive of previous experience with malaria, 2 had spent some time in endemic malaria areas overseas, and 2 were natives of the Mediterranean Coast. Four, even after persistent questioning, were certain that they had never had malaria. One was not mentally competent. All subsequently received adequate fever from other strains and species of malaria.

Seventeen of the white patients were inoculated primarily with *Plasmodium malariae* (*quartan*) because of a history which suggested previous experience with natural vivax malaria. All but 1, a Puerto Rican with a history of chills and fever, had satisfactory clinical responses, with adequate numbers of paroxysms and hours of fever. This Puerto Rican was

reinoculated with a Southwest Pacific strain of *P. vivax* and had an excellent course.

The 75 Negroes were all inoculated primarily with *P. malariae*. There was a satisfactory clinical response of more than 8 paroxysms, with temperature elevation over 103° F., in all but 7 of the cases. Of the 7 failures, 2 subsequently received adequate treatment with falciparum malaria and 4 of the remainder received hypertherm cabinet therapy. The last one, a case of asymptomatic neurosyphilis with conversion hysteria, refused further fever therapy.

Our studies have corroborated the generally accepted opinion that Negroes and individuals from the Mediterranean area are refractory to inoculations with *P. vivax*. We have also found that soldiers from endemic areas in Puerto Rico and the southeastern United States who have had a history of chills and fever, are usually unresponsive to inoculation with *P. vivax*. Such individuals should routinely be given primary inoculations with *P. malariae*.

Quantitative daily parasite counts and hourly temperature records have shown that 4 types of reactions are encountered: (1) hyperimmune, (2) immune, (3) partially immune and (4) hypersusceptible.

The *hyperimmune* individual is unusual and, from a therapeutic standpoint, is practically never encountered. An inoculation of 50 to 100 million trophozoites causes neither an elevation of temperature

nor a demonstrable parasitemia. Such a person has homologous immunity, presumably having had previous experience with the same strain of malaria.

The *immune* patient, after inoculation with several million plasmodia, subsequently develops a slight parasitemia (but not up to therapeutically activating levels) which is followed by a rapid disappearance of the parasites from the blood, and is unaccompanied by any febrile response over 100° F. This reaction was frequently encountered in colored soldiers inoculated with *P. vivax*. When found in white patients it may be taken as evidence that they have had previous experience with a homologous strain of malaria.

encing 5 or less paroxysms of fever to 103° F., and (b) those experiencing 6 to 10 such episodes. This type of response indicates that the individual had previous experience with a heterologous strain of malaria, and seldom is the clinical course sufficient to be considered a successful treatment. A certain number of these patients will evade pre-inoculation recognition and in the interest of conservation of time and morbidity they should be promptly discovered post-inoculation. The treatment with a plasmodicidal drug and re-inoculation with another species or strain of malaria should be effected upon recognition of this immune state.

Of our 208 primary vivax inoculations

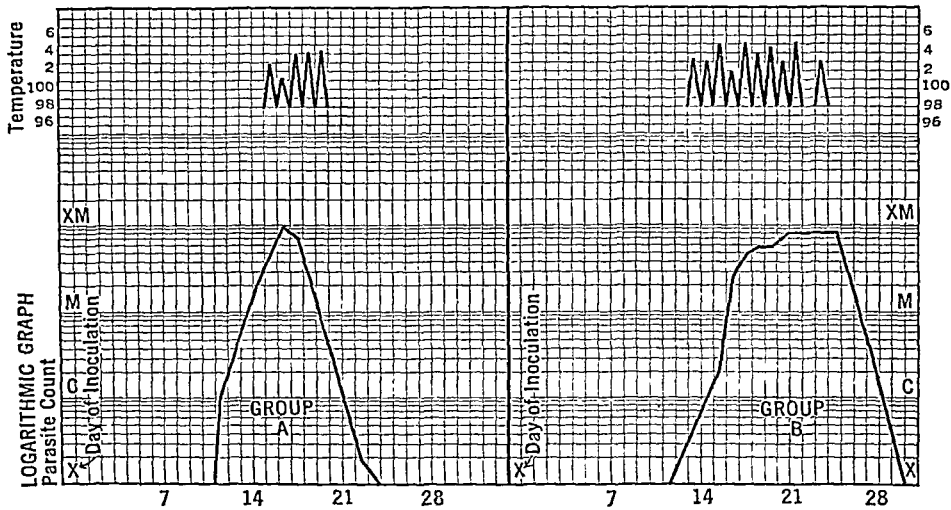


FIG. 1.—Partial immunity.

Those with *partial immunity* are a provoking problem in therapeutic malaria. Their recognition is important, and they may be discovered by eliciting a history of a previous attack of malaria before inoculating them. Parasites appear in the blood of these individuals and increase to a density of several hundred per c.mm., before any febrile response occurs. The patient experiences from 3 to 7 paroxysms of fever, whereupon the parasite count spontaneously drops precipitously and the patient becomes afebrile. Partially immune responses (Fig. 1) may be divided into 2 groups: (a) those experi-

encing 5 or less paroxysms of fever to 103° F., and (b) those experiencing 6 to 10 such episodes. This type of response indicates that the individual had previous experience with a heterologous strain of malaria, and seldom is the clinical course sufficient to be considered a successful treatment. A certain number of these patients will evade pre-inoculation recognition and in the interest of conservation of time and morbidity they should be promptly discovered post-inoculation. The treatment with a plasmodicidal drug and re-inoculation with another species or strain of malaria should be effected upon recognition of this immune state.

Of the 23 cases, 15 were in Group A and were subsequently reinoculated, 5 with

heterologous strains of vivax and 10 with quartan malaria. Eight were in Group B, of which 6 were re-inoculated with heterologous vivax and 2 with quartan. All had additional paroxysms to the therapeutic optimum with the single exception of a native of Greece. This soldier, primarily inoculated with Southwest Pacific vivax, was inoculated after his immune response thereto with quartan malaria which also failed to produce a desirable therapeutic level of fever. Falciparum malaria was finally used with excellent results.

period even after the patient becomes afebrile. These patients, whom Boyd describes as having a pristine susceptibility, may go on to a prolonged number of paroxysms unless interrupted by a plasmodicidal drug. In our series, 27 paroxysms was the highest total permitted. Boyd¹ has observed continuous clinical activity without a remission for 95 days of fever. He has found that in the hypersusceptible group the number of febrile experiences averages between 16 and 25 days before a spontaneous remission occurs. This type of reaction is illustrated

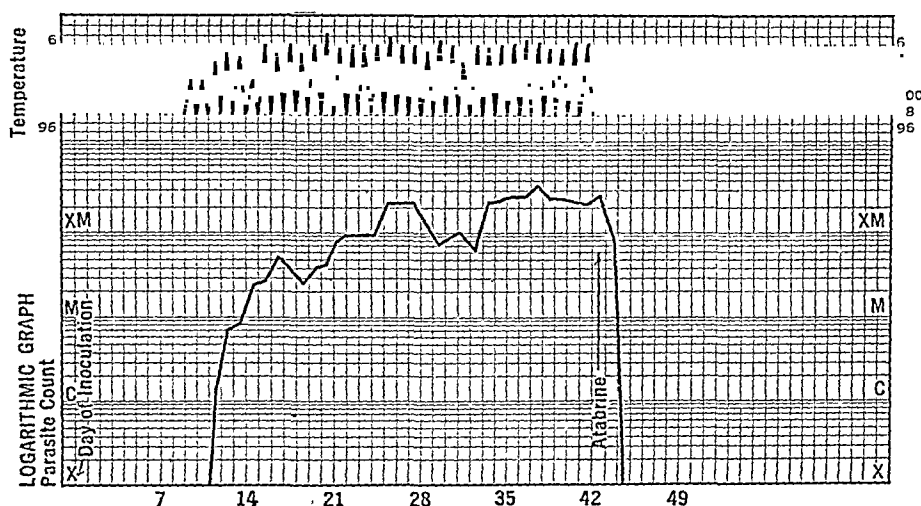


FIG. 2.—Hypersusceptibility.

Our experience has prompted us to routinely re-inoculate the patients in Group A with *P. malariae* (quartan) and those in Group B with a heterologous vivax strain. This assures, with rare exceptions, a completion of a satisfactory number of paroxysms for those in Group A. The use of a heterologous vivax strain in Group B in most instances insures a sufficient added number of febrile episodes and, because of the shorter incubation period and the quotidian or tertian cycle of the paroxysms, many hospital days are saved.

The *hypersusceptible* individual usually becomes febrile several days before parasites are microscopically discernible in the blood. The parasite count rises to a high level, which is maintained for the entire

in Figure 2 and usually indicates an initial encounter with malaria.

The daily quantitative determination of the parasite count is highly desirable. It permits the early recognition of exuberant or runaway infections and encourages the prompt institution of measures designed to terminate the therapy or to bring it within bounds. It has also been employed profitably to forecast the immune types of reaction allowing us to take appropriate steps to terminate the morbidity-producing but therapeutically unsatisfactory parasitemias. Re-inoculation with a different strain or species of malaria, as previously described, may then be performed earlier than would be otherwise

possible, thus saving valuable hospital days.

Technique. The technique of the quantitative parasite count, which is Boyd's modification of that described by Earle and Perez,² may be described in outline form as follows:

1. Materials required:

- (a) Capillary pipettes graduated to deliver 5 c.mm. of blood.
- (b) Glass slides on which are ruled or etched rectangles measuring 3 by 15 mm.
- (c) Microscope, the ocular of which contains a Howard disk micrometer, the surface of which is ruled with 1 large square, divided into 16 minor squares and so calibrated that with a predetermined tube length, the area on a slide covered by the large square on the micrometer is known.
- (d) Diluted Giemsa's stain.

will be spread over each sq. mm. of the rectangle 0.11 c.mm. or $\frac{1}{9}$ c.mm. of blood.

- (b) Stain smear in Giemsa's stain as any other thick smear, wash, drain and dry.
- (c) Assuming that calibration of the micrometer disk has shown that the outline of the large square covers 0.01 sq. mm. on a slide, when the stained smear is placed under the microscope it will be necessary to count the parasites observed in 100 consecutive and discrete fields to get a sample of the parasites in the blood spread over 1 sq. mm. The fields should be selected while transversing the smear on different parallel lines. The total of the parasites counted in 100 fields will, when multiplied by 9, give the number per c.mm. (Fig. 3.)

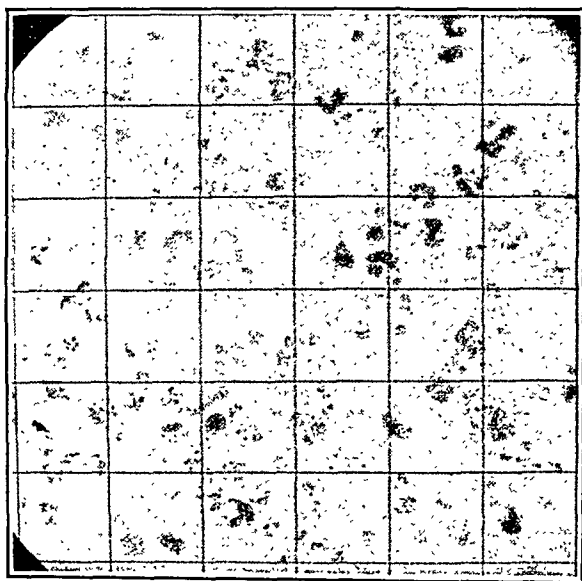


FIG. 3.—Photomicrograph ($\times 95$) with the Howard Disc of A. Thick malaria smear (*P. vivax*). Parasite count = 42,000 per c.mm.

2. Methods:

- (a) Discharge exactly 5 c.mm. of blood on the ruled rectangle of the slide, carefully avoiding bubbles. With a needle-point carefully spread the blood out to the edges and into the corners of the ruled area. Allow to stand in a horizontal position until dry. Since 5 c.mm. of blood are spread out over 45 sq. mm., there

Vivax parasitemias usually average 20,000 to 40,000 per c.mm., and rarely exceed 50,000. Quartan parasitemias involving chiefly the aged erythrocytes, rarely reach a height of 20,000 per c.mm. There is no established limit to falciparum parasitemias, but the danger line is 100,000 to 200,000 per c.mm. If a falciparum

parasitemia reaches 500,000 per c.mm., death is almost inevitable.

The use of the daily quantitative parasite count is particularly helpful in following quartan infections. The incubation period of quartan malaria averages between 12 and 15 days. A rising parasite level gives assurance that a febrile course will ensue. A parasitemia failing to exceed 3000 per c.mm. 30 days following inoculation, and in the absence of any fever above 103° F., is fairly solid evidence that the patient has a relatively high degree of immunity and that some other form of therapy is indicated. History is of no value in forecasting an

other 2 showed a low parasite count without any febrile response. This would seem to confirm the futility of using any vivax strain in the inoculation of colored people.

Falciparum malaria has been utilized by us in 3 cases as an adjunct to individuals showing immunity to both vivax and quartan. It should be used only on inescapable indications and under laboratory and clinical control that approaches the ideal. Quantitative parasite counts should be performed at least twice daily. Three-grain doses of quinine should be administered hourly as long as the temperature exceeds 104° F. or when the quantitative

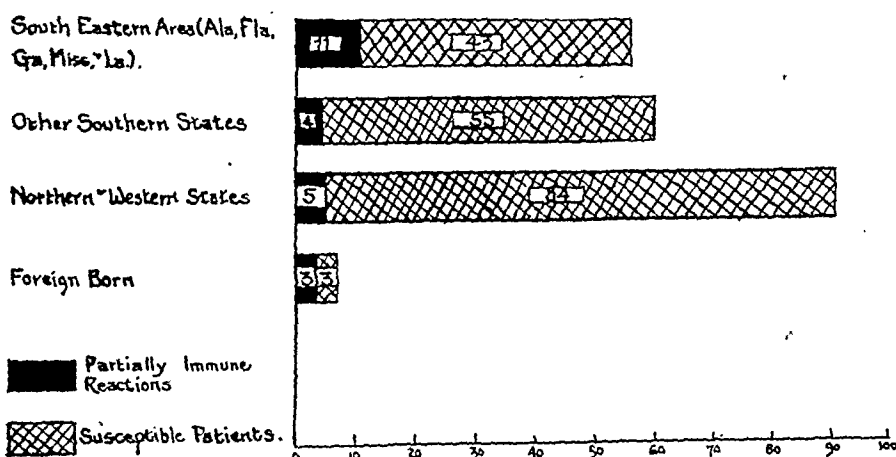


FIG. 4.—Distribution by geographic origin of 225 white patients showing number of partial immunes and susceptibles to therapeutic vivax malaria.

immune reaction in the Negro. Kroll³ reported 11% failures in the Negroes, which parallels our experience with 7 failures out of 75 soldiers treated with quartan malaria.

An attempt was made to inoculate 8 colored patients with *P. vivax*. One was given a strain indigenous to the southern United States which resulted in a hyper-immune reaction. Seven received various strains from the Southwest Pacific, 3 by mosquito transmission and 4 by intravenous blood inoculation. Of the mosquito transmissions, 1 patient had 7 paroxysms and 2 failed to develop a parasitemia. Of the blood inoculations, 1 had 3 paroxysms, another had 4, and the

parasite count is over 100,000 per c.mm. With these precautions we have been able to keep the therapy within bounds and to obtain 5 to 8 paroxysms above 103° F. before a spontaneous remission occurs.

Conclusions. 1. Three hundred members of the Army with various types of neurosyphilis were treated with therapeutic malaria. From this experience certain conclusions appear warranted.

2. Negroes should be routinely inoculated with quartan malaria.

3. Vivax malaria is a satisfactory means of inducing fever in the treatment of white patients afflicted with neurosyphilis, pro-

viding they have never had natural malaria.

4. Malaria therapists have experienced some reservations in their use of vivax in people raised in southeastern United States. Of our 43 white patients who came from this area, 80 % were susceptible. Of the 11 failures, all except 1 gave a history of having chills or fever sometime during their lives. Of those from the rest of the United States, 93 % were satisfactorily treated with *P. vivax* without notable geographic exceptions (See Fig. 4).

5. Candidates from the United States who give a history of a previous natural infection, those from the Mediterranean,

and Puerto Rico, all should be inoculated primarily with quartan malaria.

6. White individuals who experience a spontaneous remission from a primary vivax inoculation before receiving a clinically adequate amount of fever, should be re-inoculated with quartan malaria, if they have experienced 5 or less paroxysms, or a heterologous strain of vivax if they have experienced more than 5 paroxysms.

7. Daily determinations of the parasite blood level are extremely helpful in following the course of the infection as to its severity, degree of the patient's resistance, and the early forecasting of an immune response.

REFERENCES

1. BOYD, M. F.: Criteria of Immunity and Susceptibility in Naturally Induced Vivax Malaria Infections, *Am. J. Trop. Med.*, **22**, 217, 1942.
2. EARLE, W. C., and PEREZ, M.: Enumeration of Parasites in the Blood of Malarial Patients, *J. Lab. and Clin. Med.*, **17**, 1124, 1932.
3. KROLL, M. M.: Quartan Malaria in the Treatment of Neurosyphilis, *Am. J. Syph. and Ven. Dis.*, **24**, 148, 1940.

INTERFERENCE DISSOCIATION—AN EARLY FINDING IN ACUTE RHEUMATIC FEVER*

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INTERFERENCE dissociation was first described in 1915 by White.¹⁴ Dissociation of this type has been regarded as a normal finding, and as such is known merely as an expression of increased vagal tone. The condition is therefore thought to be of no particular clinical significance other than its possible confusion with heart block, which of course bears a much more serious prognosis.

During the past 2 years at our hospital we have encountered 32 cases of acute rheumatic fever, 4 of which had electrocardiographic findings of interference dissociation as an early, though transitory, finding. In 3 of these patients there was an accompanying heart block. These cases are reported in an effort to demonstrate that, although interference dissociation may in most instances be perfectly normal, at other times, it is unquestionably pathologic.

Case Reports. CASE 1. A 20 year old soldier was admitted to the hospital June 2, 1943. With a history of multiple migratory joint pains. He stated that as a child he had chorea and "heart trouble," but that subsequently he successfully passed physical examinations to enter athletic sports in high school.

Examination revealed a systolic murmur at the apex and a systolic and diastolic murmur at the base of the heart. The knee joints were inflamed. Sedimentation rate was elevated. Response to salicylates was prompt.

An electrocardiogram (Fig. 1) demonstrated interference dissociation 2 days after admission. On the following day the picture was one of increasing length of the PR interval (Fig. 2) simulating Wenckenbach periods but with no dropped beats. Subsequent

tracing 2 days later showed a PR interval of 0.22 second. This became normal on the following day. Patient was discharged, improved, after some 2 months hospitalization.

Diagnosis. (1) Acute rheumatic fever. (2) Valvular heart disease, mitral insufficiency, aortic insufficiency and stenosis, caused by previous attack of rheumatic fever.

CASE 2. An 18 year old soldier was admitted to the hospital on May 29, 1944. He gave a history of a "cold" and sore throat 3 weeks before the onset of present symptoms. Two weeks previous to that, while home on furlough he had pneumonia, from which he made an uneventful recovery. In the past several years he has had nose bleeds on the average of about once a month. Present illness began 5 days before admission, with pain, swelling of his left knee joint, and fever. There was no history of trauma, and patient denied ever having suffered with rheumatic fever.

Examination revealed some swelling, increased warmth and tenderness on motion of the left knee joint, and a somewhat irregular cardiac rhythm. No murmurs were heard. An electrocardiogram (Fig. 3) taken 2 days after admission showed interference dissociation. This persisted for some 5 days, after which rhythm became regular.

Sedimentation rates were elevated for about a month.

Clinical course showed progressive improvement and patient was discharged after some 6 weeks.

CASE 3. A 22 year old soldier was admitted to the hospital Oct. 30, 1943, and discharged Jan. 14, 1944. He gave a history of migratory joint pains, swelling and tenderness on motion for some 2 weeks before admission. Patient denied any previous similar illness.

Examination revealed some swelling, redness and tenderness of left knee joint. There were no unusual cardiac findings. An electro-

* The meaning of this special use of the term "interference dissociation" can be found under Comment on p. 690—Ed.

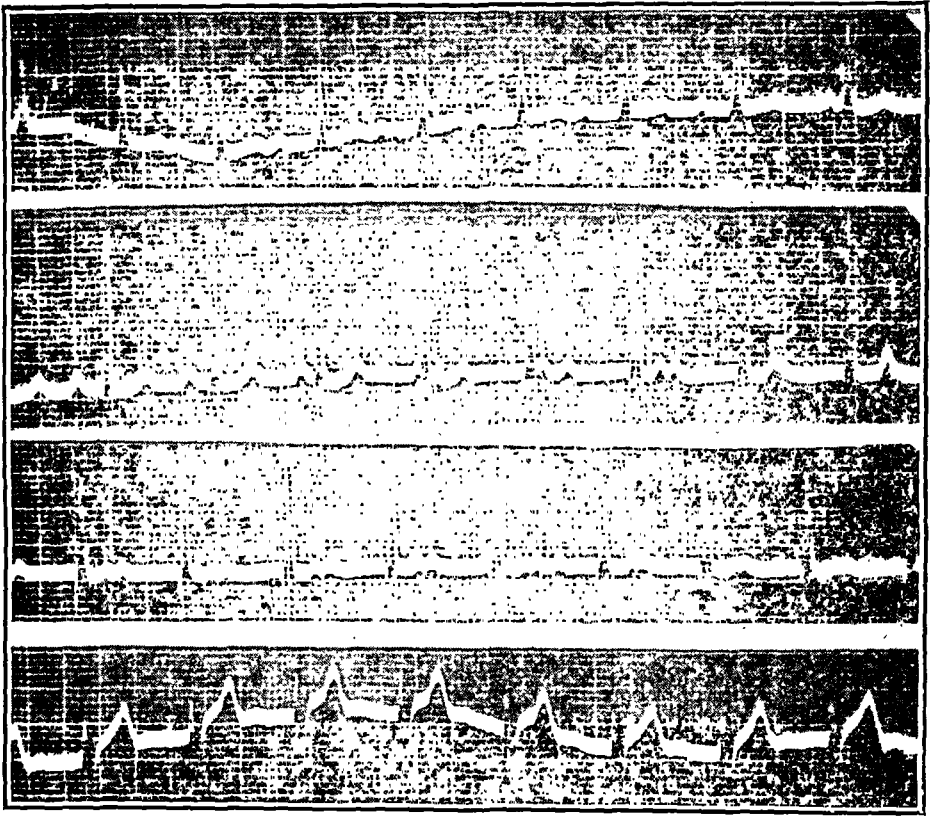


FIG. 1.—Case 1. Interference dissociation; ventricular rate 100 per minute; auricular rate 94 per minute.

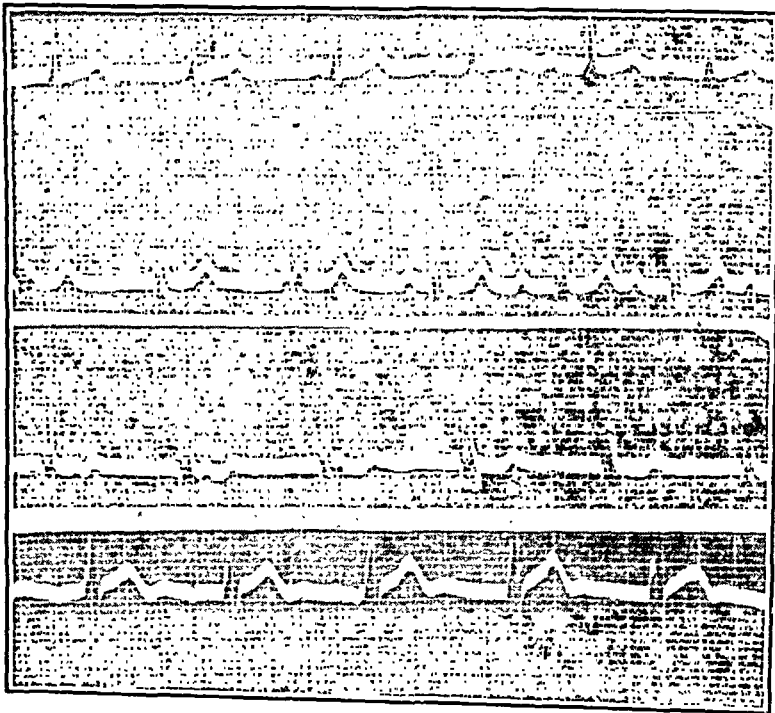


FIG. 2.—Case 1. Note in Lead 2, the increasing length of the PR intervals.

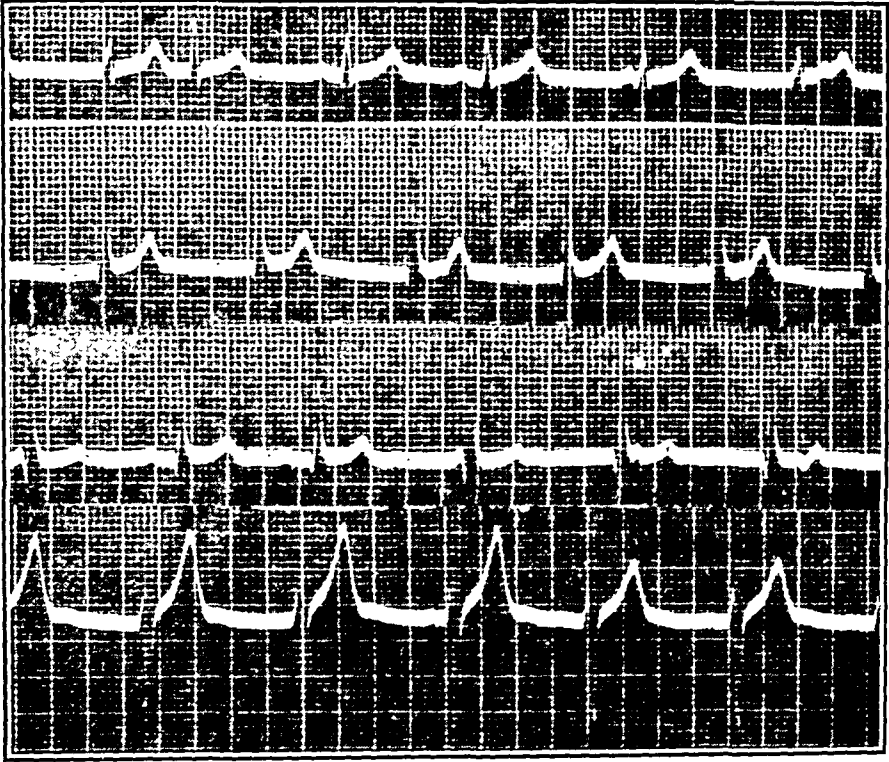


FIG. 3.—Case 2. Interference dissociation; ventricular rate 75 per minute; auricular rate 62 per minute.

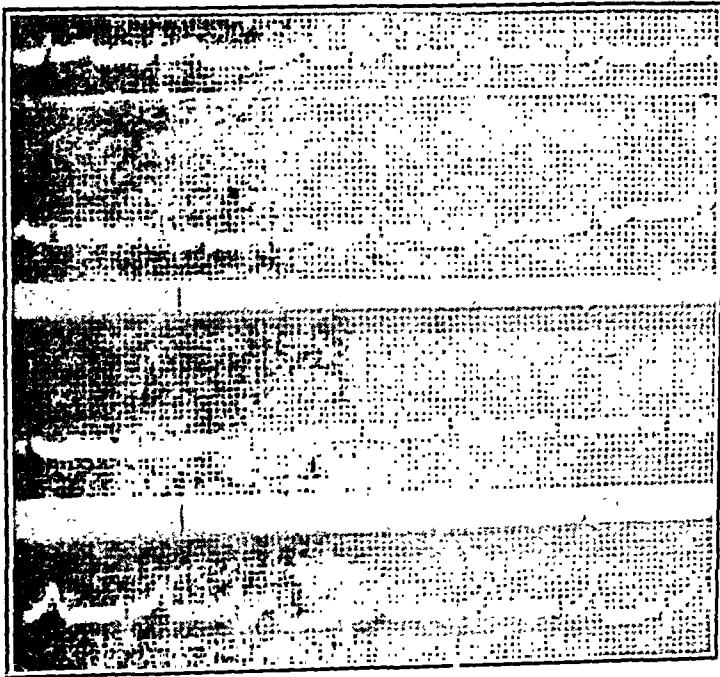


FIG. 4.—Case 3. Interference dissociation; ventricular rate 88 per minute; auricular rate 80 per minute.

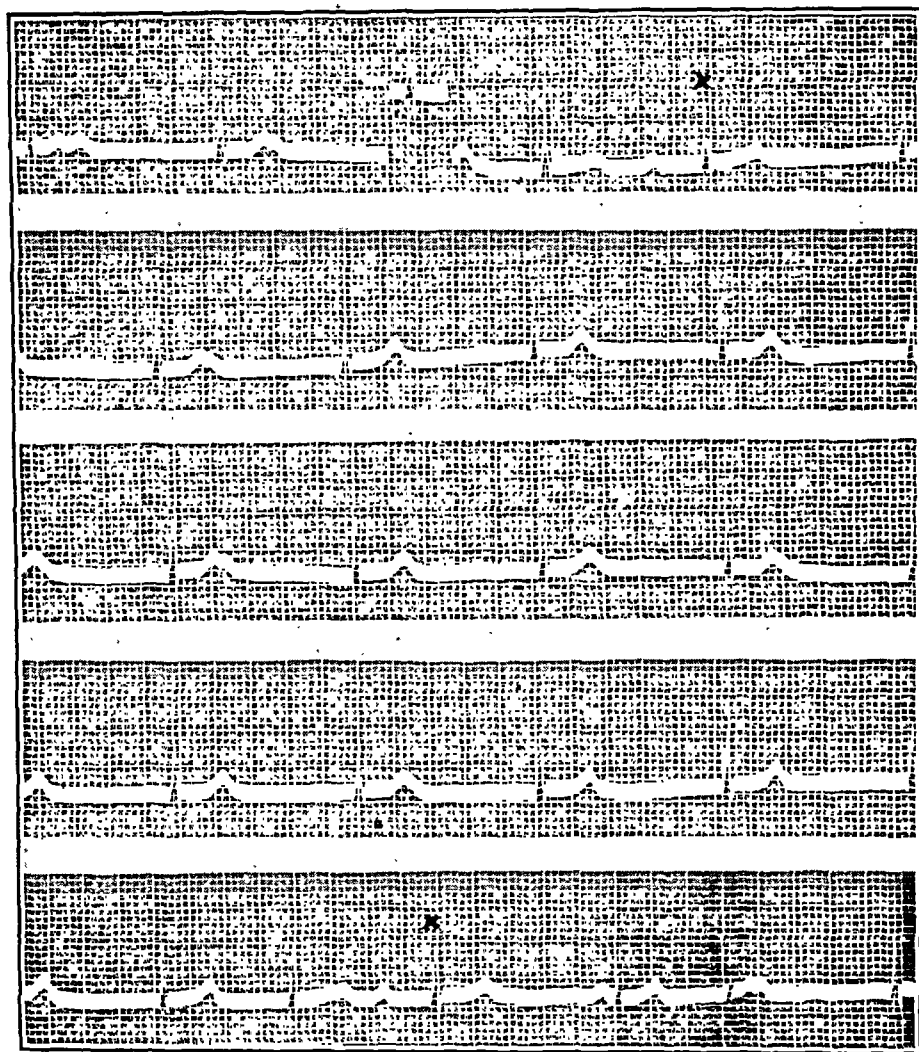


FIG. 5.—Case 4. Lead 2 taken on day after admission: shows interference dissociation and sinus arrhythmia. Several conducted beats are noted (x) with PR interval of 0.30 second.

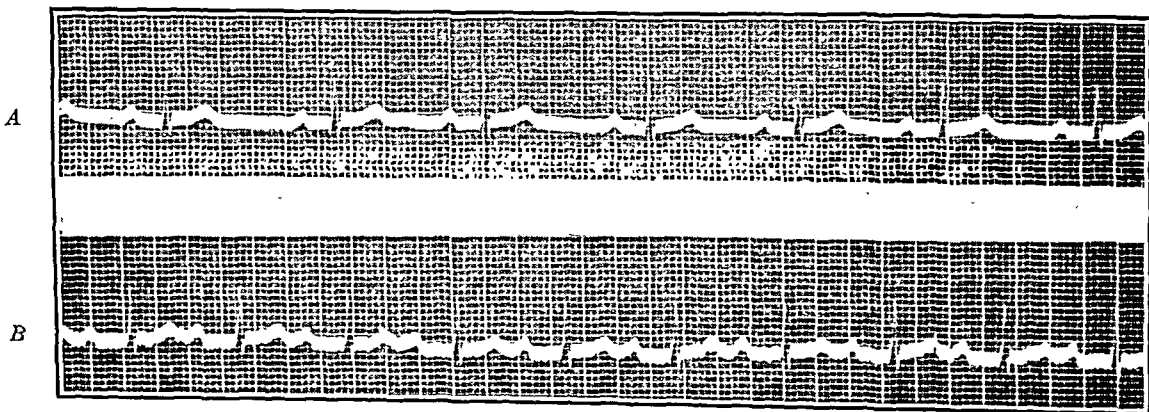


FIG. 6.—Case 4. A, Lead 2: shows the effect of exercise on Case 4 taken immediately after Figure 5. Dissociation has disappeared and PR interval is 0.24 second. B, Lead 2: following atropine sulfate gr. 1/37 subcutaneously, the dissociation disappeared. PR interval is 0.30 second. A and B demonstrate part played by the vagus in the production of interference dissociation.

cardiogram (Fig. 4) on admission demonstrated interference dissociation. These findings disappeared after 2 days. The prolongation of the PR interval endured for 5 days. Sedimentation rates remained elevated for 5 weeks.

Clinical course was one of progressive improvement, and patient was discharged after 2 months of hospitalization. At this time cardiac examination and electrocardiograms were normal.

CASE 4. An 18 year old soldier who entered the hospital on March 23, 1945 with the history of fever and migrating painful swollen joints for 6 days. He was not acutely ill on admission. The only positive findings consisted of a "hot" left knee joint and a slight irregularity to the cardiac rhythm. He showed a splendid response to salicylates and was symptom-free in a few days, although the sedimentation rate remained elevated for about 2 months. There was no evidence of valvular involvement upon discharge and Roentgen rays of the heart were normal.

Electrocardiographic Studies. On the day of admission the tracing (Fig. 5) showed interference dissociation superimposed on first degree heart block with sinus arrhythmia. This persisted for 3 days. The effect of exercise and atropine is shown in Figure 6, A and B. Dissociation was abolished and first degree heart block (0.30 second) was present. This indicated the fundamental rôle played by the vagus in dissociation of this type. Apparently the underlying picture was one of first degree heart block on which additional vagal effect produced the phenomenon of dissociation. When the latter was removed as by atropinization or through exercise, the heart block persisted.

Comment. In cases of marked sinus arrhythmia or sinus bradycardia there may be an unusually long pause between sinus impulses. The junctional tissues, the auriculo-ventricular node, or the ventricles, acting as a safety valve may take up the function of pacemaker and initiate an impulse. This is known as a nodal or ventricular escape. It is distinguished from a premature contraction in that it is not premature. A series of such beats is known as dissociation. Any sinus impulses now appearing may find the auric-

ulo-ventricular node and ventricular musculature in a refractory state; therefore the term interference. The auricles and ventricles now beat independently of each other. Interference dissociation can therefore also be termed "double rhythm." Although retrograde block is present, sinus impulses can activate the auriculo-ventricular node and ventricles should they arrive when these tissues are no longer refractory. At this time "P" waves will be visible in the usual position and shape preceding the QRS complex and the PR interval will usually be within normal limits but may be prolonged. At this time the R wave may appear earlier or it, together with succeeding T wave, may be of a different configuration than the preceding ones. The picture may, therefore, be one of seemingly complete auriculo-ventricular dissociation interspersed with beats of sino-auricular origin.

Interference dissociation can occur not only due to faulty sinus mechanism but also at a time when the auriculo-ventricular node or the ventricles become hyper-irritable. The sino-auricular node may be depressed by pressure on a hyperactive carotid sinus,¹⁵ and by digitalis medication.^{4,6,15} The auriculo-ventricular node becomes hyper-irritable and then assumes the rôle of pacemaker in infectious states⁹ and following the administration of atropine^{6,15} especially in its initial immediate effect.

Incidence in Rheumatic Fever.—There have appeared few reports of the presence of interference dissociation in rheumatic fever. In Dressler's⁴ experience this disturbance in rhythm occurs in the course of acute articular rheumatism. Cutts quotes Oettinger and Neslin's⁹ series of 7 patients with acute rheumatic fever and also report 7 cases of their own. In a footnote these authors add that they later observed the occurrence of this electrocardiographic picture in 14 out of 200 patients with rheumatic fever. Wendkos and Noll¹³ studied 100 consecutive cases of acute rheumatic fever and found 6 cases of auriculo-ventricular dissociation

with associated first degree heart block. Sigler¹² illustrates a case of acute rheumatic carditis with interference dissociation. Our series of 4 cases in 32 patients with rheumatic fever seems quite representative.

Duration. This electrocardiographic phenomenon in our cases did not endure for more than 5 days. This is in accord with the experience of others,¹³ although it has been known to persist for as long as 16 days.³

Diagnosis. The diagnosis of interference dissociation cannot be made on clinical grounds, although auscultation may reveal an irregularity of the cardiac rhythm similar to that heard with premature contractions or second grade heart block. It is only the electrocardiogram on which we can depend for the diagnosis. The confusing feature here may be the picture of heart block. The main distinction between heart block and interference dissociation is that in the latter, the ventricular rate is either equal to or greater than that of the auricles. In heart block the reverse is true.

Interference dissociation is asymptomatic. None of our patients had any complaints which might be attributed to this cardiac disturbance. It is reasonable, however, to suppose that, particularly in a hypersensitive individual, sensations as of a "skipped" beat might be complained of. Wilson¹⁶ had 3 patients who complained of intense palpitations during experimentally induced auriculo-ventricular rhythm.

The finding of interference dissociation in our cases had no bearing on their later course. All of our patients recovered, and were at no time dangerously ill. The 1 with valvular involvement had contracted these deformities from a previous attack of this same disease. Once a doctor has ruled out complete heart block he can feel safe in offering the patient's family a good prognosis as to the early disappearance of this electrocardiographic abnormality. Wendkos and Noll¹³ arrive at the same conclusion. This, however,

is at variance with Cutts³ who is in full agreement with Richardson's opinion¹⁰ "auriculo-ventricular rhythm is not in itself fatal, but is frequently associated with severe infection or severe and chronic heart disease."

Importance. Interference dissociation has been generally considered a normal finding. Katz⁷ states that it is not evidence of heart disease, and merely bears the same connotation as simple sinus arrhythmia. He considers it an expression of a "natural cardiac mechanism which comes into play to offset the consequences of marked sinus arrhythmia." However, one must doubt that this is always so. The disturbance of the cardiac rhythm, particularly as seen in our cases of rheumatic fever, associated with the well-known prolongation of the PR interval, is surely indicative of some pathologic state. It is conceivable that in certain cases of acute arthritis or fevers of undetermined origin, the finding of interference dissociation may be of aid in establishing the diagnosis.

Pathological Physiology. The basic physiological pathology may be inflammatory; that is, due to some localized myocarditis. If that is so, the transitory electrocardiographic picture may be caused by edema which is rapidly absorbed. The rôle of the vagus may be an important one. Stimulation of this nerve may be either central or peripheral. The release of the vagus by means of exercise or the administration of full doses of atropine as was performed in Case 4 indicates that at least in this instance it was a dominant factor in the production of the dissociation.

"Double rhythm" bears some analogy to the increased auriculo-ventricular conduction time. The latter is the most frequent abnormality encountered in rheumatic fever.¹¹ It is due to transient edema around a few small rheumatic nodules in the myocardium according to Boyd.¹ However, the vagus must play some rôle in the production of this heart block. In 2 of Wendkos and Noll's cases¹³ they were able to abolish this conduction disturbance

by the administration of 2.5 mg. atropine sulphate. Bruenn² obtained similar results in 19 out of 22 cases of prolonged PR interval due to rheumatic fever, by paralyzing the vagus with atropine given intravenously. He suggested that the focus of vagal irritation lay in the medulla.

Keith⁸ investigated this subject in some detail. He studied a group of children with rheumatic fever, together with a control series, and he concluded that in this disease there is overstimulation of the vagus nerve resulting in prolongation of the PR interval. In his opinion the site of overstimulation of the vagus lay in its termination in the heart rather than in the medulla. As evidence for this theory of overstimulation of the vagus he describes cases of rheumatic fever with prolongation of the PR interval, which prolongation was markedly diminished by the administration of atropine in contradistinction to a control group where atropine had little effect.

In this article Keith quoted Gross and Fried⁵ who designated certain local pathologic changes as the cause of the conduction time prolongations. These pathologic changes occurred in small arteries and consisted of a variety of inflammatory and vascular phenomena, including cellular infiltration of the node and surrounding tissues, edema, and destruction of collagen. Gross and Fried found exudative or vascular changes in the node and bundle tissues in approximately 66% of active cases. Keith admitted that this explanation was the most widely accepted theory,

but feels that it was only applicable to the severe cases that have died of the disease, and that it did not furnish a satisfactory explanation in the mild cases referred to in his study.

Considering that in our cases of acute rheumatic fever there were found both "double rhythm" and heart block, and both of transient occurrence, it is reasonable to assume that the basic pathology in these cases of rheumatic fever is similar if not identical. In both, overactivity of the vagus nerve undoubtedly exists.

Summary and Conclusion. 1. Four cases of interference dissociation which occurred early in the course of rheumatic fever are presented.

2. A discussion of the underlying physiological-pathology is made, and a review of the literature undertaken. Interference dissociation in these cases of rheumatic fever is taken to be an expression of hyperfunction of the vagus nerve.

3. The similarity between first degree heart block and interference dissociation is pointed out. In certain questionable cases it may prove helpful in establishing a correct diagnosis, just as the finding of a prolonged PR interval is significant.

4. Although the findings of interference dissociation in rheumatic fever is a transient one, and probably bears no relation to the future outcome of the case, it must not be regarded as an expression of the natural cardiac mechanism in all cases; but in certain instances, it is of definite pathologic significance.

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REFERENCES

1. BOYD, WM.: *Pathology of Internal Disease*, 2d ed., Philadelphia, Lea & Febiger, 1935.
2. BRUENN, H. G.: *The Mechanism of Impaired Auriculo-ventricular Conduction in Acute Rheumatic Fever*, *Am. Heart J.*, **13**, 413, 1937.
3. CUTTS, F. B.: *The Transition Between Normal Sinus Rhythm, Ventricular Escape, Auriculo-ventricular Nodal Rhythm, and Auriculo-ventricular Dissociation*, *Am. Heart J.*, **13**, 453, 1937.
4. DRESSLER, W.: *On the Question of the Origin of Interference Dissociation and of the Retrograde Conduction of Ventricular Extrasystoles*, *Wien. Arch. f. inn. Med.*, **19**, 611, 1930.
5. GROSS, L., and FRIED, B. M.: *Am. J. Path.*, **12**, 31, 1936.
6. HEWLETT, A. W.: *Case Showing Rapid Ventricular Rhythm with Periods of Auriculo-ventricular Dissociation*, *Heart*, **10**, 9, 1923.
7. KATZ, L. N.: *Electrocardiography*, Philadelphia, Lea & Febiger, 1941.
8. KEITH, J. D.: *Overstimulation of the Vagus Nerve in Rheumatic Fever*, *Quart. J. Med.*, **7**, 25, 1938.

9. OETTINGER, I., and NESLIN, W.: *Über Atrioventikuläre Automotie bei Rheumatischer Karditis*, *Deutsch. Arch. f. klin. Med.*, **173**, 212, 1932.
10. RICHARDSON, H. B.: *Auriculo-ventricular Rhythm and Digitalis*, *Arch. Int. Med.*, **16**, 517, 1915.
11. ROTHSCHILD, M. A., SACHS, B., and LIBMAN, E.: *The Disturbances of the Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever*, *Am. Heart J.*, **2**, 356, 1927.
12. SIGLER, L. R.: *The Electrocardiogram*, New York, Grune & Stratton, 1944.
13. WENDKOS, M. H., and NOLL, J.: *A Survey of Rheumatic Fever in a Large Station Hospital*, *Med. Clin. North America*, **28**, 124, 1944.
14. WHITE, P. D.: *A Study of Atrioventricular Rhythm Following Auricular Flutter*, *Arch. Int. Med.*, **16**, 517, 1915.
15. WHITE, P. D.: *Ventricular Escape with Observations on Cases Showing a Ventricular Rate Greater Than That of the Auricles*, *Arch. Int. Med.*, **18**, 244, 1916.
16. WILSON, F. N.: *The Production of Auriculo-ventricular Rhythm in Man After the Administration of Atropine*, *Arch. Int. Med.*, **16**, 989, 1915.

CHANGES IN THE CARDIOVASCULAR SYSTEM IN SCRUB TYPHUS IN EARLY CONVALESCENCE

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BECAUSE of its prevalence in areas of the Southwest Pacific and the CBI Theaters where large numbers of troops have been stationed, scrub typhus fever has become a disease of considerable importance. Its severity and mortality varies with the locality in which it is met, but in general, and for reasons not entirely understood, prolonged disability is common.

The clinical picture in a large proportion of the patients who have recovered from the disease is as characteristic as the headache, swinging temperature, rash, and eschar seen in the acute illness. These patients are profoundly weak, sleep poorly, perspire excessively, are irritable, and often have a low grade temperature elevation. When at rest the pulse rate is quite rapid, and with exercise dyspnea, palpitations, precordial pain, and syncope are common. Contrary to what might be expected, these symptoms may be out of all proportion to the severity of the acute illness.

Superficially at least the subjective complaints and clinical abnormalities which are observed during convalescence seem related to the cardiovascular system. As a consequence patients are often hospitalized with a diagnosis of chronic myocarditis or myocardial insufficiency the result of scrub typhus. On those occasions when a murmur is heard physicians have attributed valvular damage to the rickettsial infection. Finally, and in complete contrast, instances have been observed where the persistent tachycardia and poor tolerance for exercise have been attributed to an anxiety state entirely independent of any organic ailment.

This apparent confusion in the minds of physicians who have contacted patients recently recovered from scrub typhus fever emphasizes the need of an evalua-

tion of the potential and actual cardiovascular sequelæ of the disease. Is scrub typhus unusual in its involvement of the endocardium or the myocardium? If so, how much impairment of cardiac function is to be expected? If the heart is not involved, what is the basis of the tachycardia at rest, the inability to tolerate exercise without dyspnea, and, in some instances, the actual precordial pain? A proper answer to these questions not only clarifies the problem of therapy, but will prevent a patient from unjustifiably being labeled a cardiac cripple through the misuse of such terms as myocarditis, or valvular disease.

Accordingly, an attempt was made in this study to establish the type and extent of cardiovascular dysfunction in a representative group of patients who had recently recovered from scrub typhus fever.

Material. One hundred patients, ranging in age from 19 to 35 years, were examined on the average of 49 days after the onset of the acute illness. The study included an analysis of the subjective symptoms, a physical examination, an exercise tolerance test in a limited number of instances, and at least 1 electrocardiogram on each patient.

The group was a fair cross-section of a larger one that had contracted the disease in a Southwest Pacific base where the mortality was low. With few exceptions the men were not seen during the acute illness, but only after they were well enough to have been evacuated from the forward area. Nevertheless, it was evident that few had had a particularly stormy course. This is best illustrated by the fact none had been in coma, only 1 had been given oxygen therapy, and the total febrile period for the group averaged

9 days, or roughly 5 days less than is normally expected.

The diagnosis of scrub typhus was based upon the intractable headache, remitting temperature, rash, eschar, and positive agglutination for *Proteus* OXK in titers of 1:160 or higher. All of these diagnostic features were not present in each case. The absence of an eschar, for example, or a negative agglutination was not considered sufficient evidence to negate the diagnosis since either or both findings may be lacking when the clinical picture is so characteristic as to be unmistakable. It is possible that some of the patients with negative agglutinations may have shown a positive test at a later date for this is known to happen as late as two months after the initial infection. Under the circumstances of this study, however, it was not possible to check the test indefinitely. Selection of the patients was such that only 6 did not have either an eschar, or a positive agglutination.

Each of the patients was interviewed by the same examiner who recorded the outstanding complaints, tabulated an average of the daily pulse rate and blood pressure, and performed the physical examination. With 1 exception, each patient had been ambulatory for at least 14 days before he was examined. In many instances repeated interviews were necessary.

In all cases at least 1 electrocardiogram was obtained with the patient at rest, and where important abnormalities were observed tracings were repeatedly taken as long as the individual was under observation.

A two-step exercise tolerance test was taken by 25 of the group. The technique was essentially that outlined by Master.³

Results. Complaints related to the cardiovascular system were noted in 30% of the group. In 21 of these patients the outstanding symptom was a rapid heart beat even when at complete rest. Dyspnea and precordial pain with effort was a common secondary ailment. Of the 9 who made no mention of a rapid pulse, 4 were

dyspneic on effort, 3 had precordial pain and syncope, and 2 were troubled with palpitations.

The average daily pulse rates for these patients was 107, and in but 2 instances was the rate below 100. Of the 70 who either felt well or did not complain of cardiovascular symptoms only 4 were found to have a daily pulse rate that averaged over 100.

It is apparent, then, that in 70% of those in whom cardiovascular disease was suspected tachycardia was an important complaint and could be objectively proven in practically all instances, while in the others it was infrequently noted.

No important abnormalities in blood pressure were seen in any of the patients, readings ranging from 104 to 138 mm. Hg systolic, and from 60 to 90 diastolic.

The precordial pain mentioned by many as occurring during effort was piercing in character, transient, not transmitted, almost invariably localized over the left nipple, and usually aggravated by taking a deep breath. Although it is not possible to state what factors are responsible for this pain there was only a superficial similarity to angina pectoris in the several patients observed during an attack.

The 25 who took the exercise test were a mixed group of symptomatic and asymptomatic patients. In 12 the pulse rate did not return to within 10 beats of the resting level at the end of 2 minutes. All but 1 of these had so-called cardiovascular symptoms, and in 6 of those the blood pressure also failed to return to normal levels.

During the exercise tolerance test a considerable number complained of dyspnea, but in no instance was this associated with any marked degree of cyanosis, and the lungs were clear on auscultation.

On auscultation a murmur was heard in 6 of the symptomatic group and in 2 patients who had no complaints. All the bruits were systolic. The point of maximum intensity of 6 of the murmurs was at the pulmonic area, while the remaining 2 were heard best at the mitral area. In

only 1 case was the murmur of a greater intensity than Grade 2 and this patient had a definite mitral lesion the result of rheumatic fever. A diastolic murmur was not heard in any of the patients.

Evidence of cardiac failure, such as hepatomegaly, peripheral edema, and pulmonary congestion was not found; in only 1 instance was an abnormal rhythm, other than sinus arrhythmia, detected, and this was caused by an occasional auricular ectopic beat.

a second degree heart block was critically ill, and had been given an unknown quantity of digitalis in the forward area. One week later, when normal auriculo-ventricular conduction had been restored, the T waves in leads 2 and 3 were sharply inverted, but not suggestive of a digitalis effect. With complete recovery the tracing was normal.

The remaining patients, including the 3 with delayed ventricular conduction, and 1 each with negative T waves in leads 2

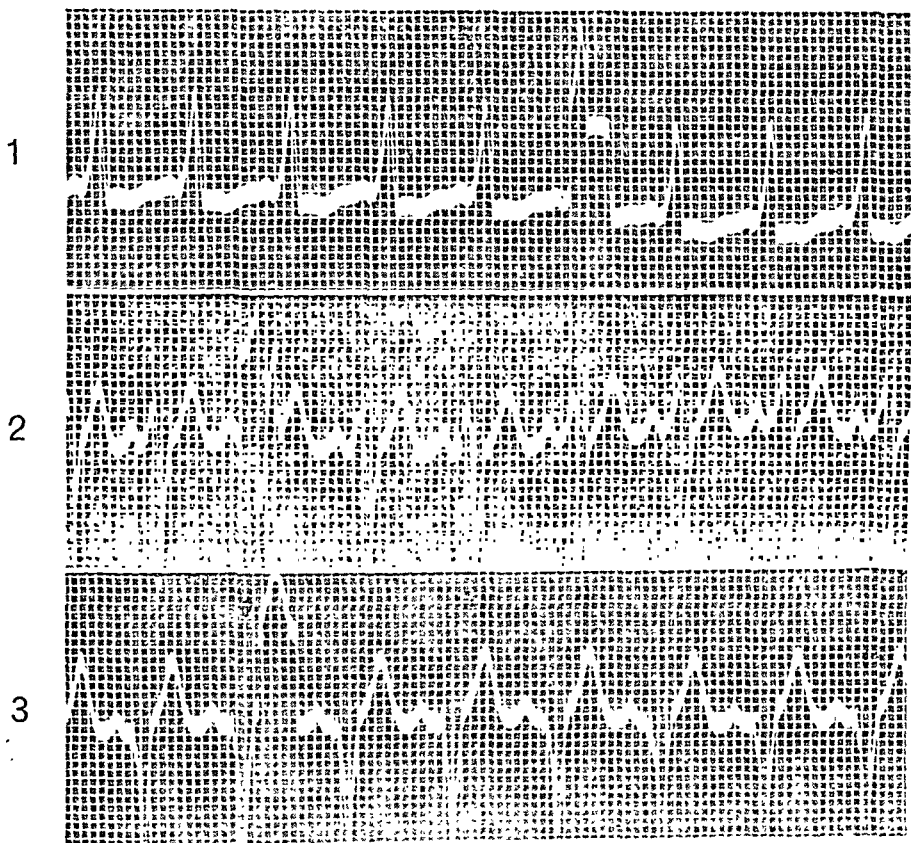


FIG. 1.—Left bundle branch block in a patient 22 years of age 43 days after the onset of scrub typhus fever.

Electrocardiographic abnormalities were detected in 10 patients all of whom were in the symptomatic group. Variations from the normal included: bundle branch block, 2; intraventricular block, 1; negative T waves in 2 or more leads, 3; splintering of the QRS without increase in duration, 3; and second degree heart block, 1.

In 5 instances the changes were transient. When first seen, the patient with

and 3, and marked slurring and splintering of the QRS in lead 2 without prolonged conduction time, continued to show such abnormalities at the time this study was concluded. None had been taking digitalis or allied drugs, and the last electrocardiogram was obtained on the average of 47 days after the onset of the illness.

Figures 1 to 4 are examples of the

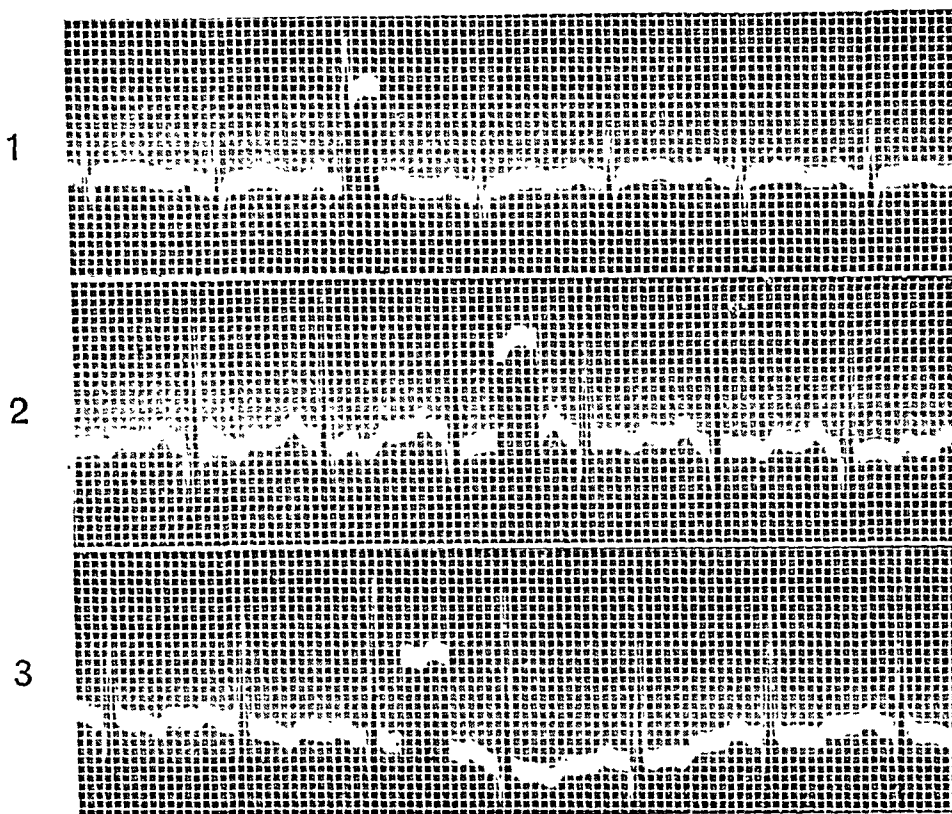


FIG. 2.—Negative T₂ and T₃, in addition to Q₂ and Q₃ in a patient 24 years of age 48 days after onset of scrub typhus fever.

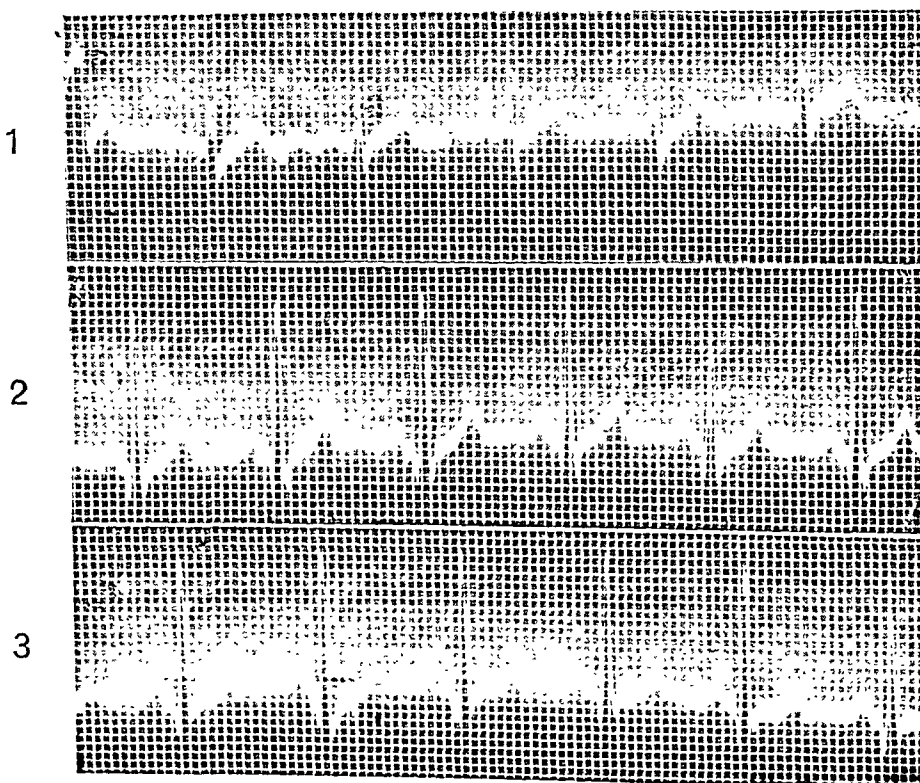


FIG. 3.—QRS duration of 0.11 second in addition to depressed ST segments in Leads 2 and 3 in a patient 21 years of age 47 days after the onset of scrub typhus fever.

electrocardiographic abnormalities which persisted.

Discussion. Woodward and Bland,⁴ discussing the effects of typhus fever upon the cardiovascular system, state that "no serious disturbance of cardiac function *per se* appeared to be responsible for the circulatory phenomenon—and transient electrocardiographic abnormalities were probably comparable to similar findings in patients seriously ill with pneumonia, and with typhoid, and with uremia."

lungs, and skin are most frequently involved. About the area of perivasculitis there may be an accumulation of monocytes, plasma cells, and lymphocytes. In the more severe cases, fragmentation and necrosis of the muscle fibers of the heart may be seen, and the edematous interstitial tissue is studded with the infiltrating cells. At least some of the myocardial degeneration may be due to the thrombosis of the smaller vessels caused by the endo- and perivasculitis.

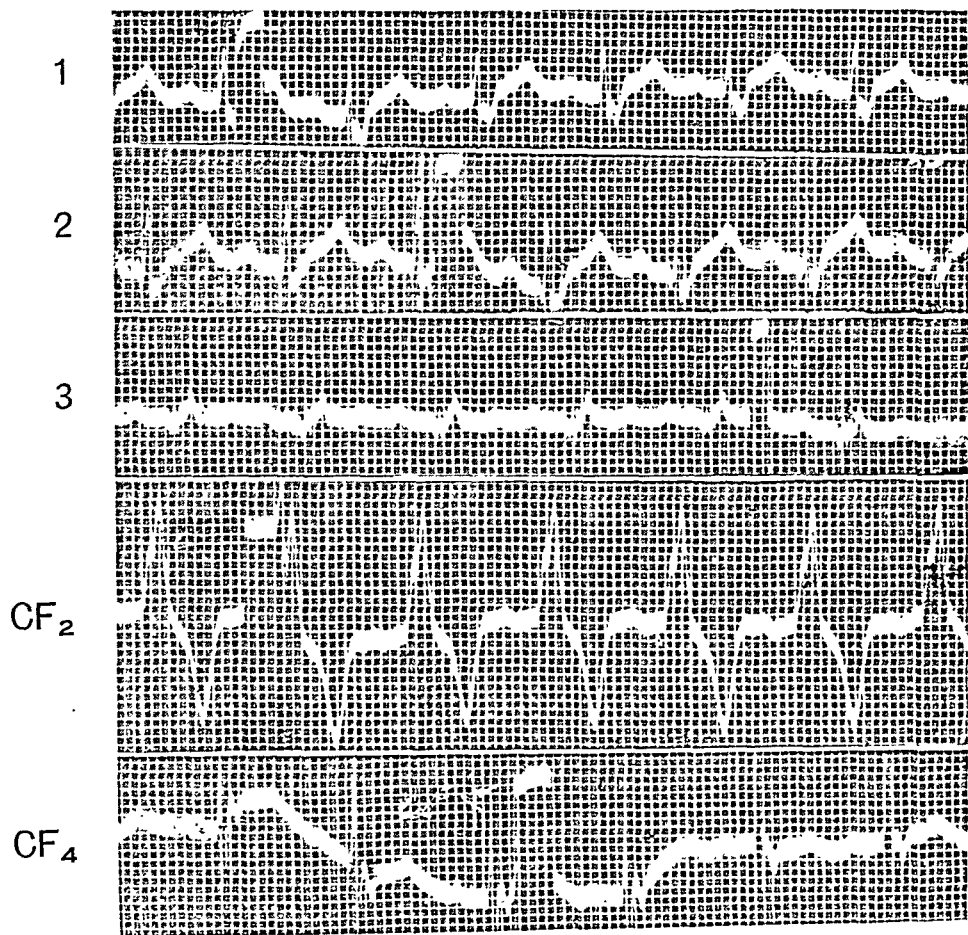


FIG. 4.—Right bundle branch block in a patient 27 years of age 46 days after the onset of scrub typhus fever.

Although the above statement was made in direct reference to acute epidemic typhus, the lesions in both rickettsial infections is somewhat similar. This consists primarily of a perivasculitis of the smaller blood-vessels. The heart, brain,

The myocardium, then, can be extensively involved and in a specific manner which is in sharp contrast to the non-specific changes following pneumonia, typhoid, and similar severe infections. When such changes are sufficiently diffuse,

or by chance involve areas of the heart particularly essential to normal function, such as the conduction system, the disease may not be without serious consequences.

For the period of time included in this study it is possible to draw only limited conclusions. As would be expected from the pathology of the disease, scrub typhus does not cause valvular damage. At least this was found to be the case two months after the initial infection. Examination of a considerably larger group than is included in this report further bears out that contention. When murmurs are heard, they are of low intensity, always systolic, more often heard at the base than at the apex, and are probably related to an increase in blood velocity incidental to the tachycardia with which they are usually associated.²

Although a considerable proportion of the patients claimed symptoms that seemed to indict the cardiovascular system, certain of those complaints, most notably precordial pain and syncope, were probably independent of any true cardiac disability. Furthermore, aside from tachycardia, it is apparent that the physical examination in the symptomatic group was negative. As an indication of organic heart disease, too much reliance cannot be placed upon the failure of the pulse or blood pressure to return to resting levels 2 minutes after a two-step exercise test. Similar results have been noted in constitutional states such as neurocirculatory asthenia.³

It appears that the type and extent of myocardial involvement following scrub typhus is best appreciated through a study of electrocardiographic abnormalities. Certain of the changes, such as delay in auriculoventricular conduction, negative T waves, and QRS slurring may be transient, although occasionally they may persist for a considerable time after the initial infection. Although those instances of intraventricular conduction defects represent either widespread myocardial involvement or an unfortunate localization of a more discrete lesion,

further study may prove that even such significant changes may be of a transient nature as is the case following other types of acute infection.

In this study the abnormal electrocardiograms were obtained from individuals in the symptomatic group, but at the same time it was impossible to predict from subjective complaints alone which of these patients would show such changes. This may be explained on the theoretical basis that many with normal electrocardiograms had cardiac lesions so located as not to distort the heart's electrical pattern. It is more probable that these patients did not have any heart disease, and their complaints were more closely related to the asthenic state which followed the long febrile and toxic illness. Nevertheless, it is of particular importance that in this study 1 in 3 of the individuals with either tachycardia, dyspnea, precordial pain, or syncope did show an abnormal electrocardiogram, and 1 in 10 had considerable involvement of the intraventricular conduction system. Finally, abnormalities were not seen where there were no symptoms.

A better understanding of scrub typhus fever should follow the realization that the disease may result in myocardial injury. Within limits, an estimation of these effects and a better defined prognosis may be obtained by means of an electrocardiogram during the acute and recovery stages. Of equal importance is the fact that the so-called cardiovascular symptoms occur when heart disease cannot be demonstrated. In such instances, and until a longer follow-up study answers the problem more completely, the use of the terms chronic myocarditis or myocardial insufficiency is an unwise presumption.

Summary and Conclusions. 1. A study was made of 100 patients on the average of 49 days after the onset of scrub typhus fever. It included an analysis of the subjective symptoms, physical examination, a limited number of exercise toler-

ance tests, and at least 1 electrocardiogram on each patient.

2. Symptoms which were apparently related to a dysfunction of the cardiovascular system and which included tachycardia at rest, dyspnea and precordial pain following exercise, and syncope were found in 30% of the patients.

3. No evidence of cardiac failure or organic valvular disease was noted in any of the patients; but tachycardia was an actual finding in practically all of the symptomatic group, whereas in the others it was infrequently observed.

4. Of 12 patients showing an abnormal response to the two-step exercise test, 11 were in the symptomatic group; but this test was thought to be inconclusive evidence of organic heart disease.

5. Ten patients showed abnormal electrocardiograms and each of these was in the symptomatic group. In 5, where there was either delayed auriculoventricular conduction, negative T waves in 2 or more leads, or slurring of the QRS complex without prolonged duration, the changes were transient.

6. The most significant electrocardiographic changes were observed in 3 patients who had either bundle branch or intraventricular block, which persisted over the period included in this study.

7. No explanation can be made as to the cause of symptoms relative to the cardiovascular system in those cases where there was no objective evidence of heart disease.

REFERENCES

1. LEVINE, S. A.: The Systolic Murmur: Its Clinical Significance, *J. Am. Med. Assn.*, **101**, 436, 1933.
2. LEVINE, S. A., and LIKOFF, W.: Some Notes on the Transmission of Heart Murmurs, *Ann. Int. Med.*, **21**, 298, 1944.
3. MASTER, A. M.: The Electrocardiogram and the Two Step Exercise: A Test of Cardiac Function and Coronary Insufficiency, *AM. J. MED. SCI.*, **207**, 435, 1944.
4. WOODWARD, T. E., and BLAND, E. F.: Clinical Observations in Typhus Fever, *J. Am. Med. Assn.*, **126**, 287, 1944.

AN 18-HOUR CONCENTRATION TEST OF KIDNEY FUNCTION

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A SIMPLIFIED concentration test of renal function has been used at this University Hospital and has been found satisfactory for clinical use. It is based on the principles of the 38 hour concentration test of Lashmet and Newburgh,² which imposes a maximal strain on the kidneys in order to secure the most concentrated urine specimen possible. The new test is performed over a period of only 18 hours and does not require the use of special diet. It entails little hardship for the subject and is particularly convenient for use on ambulatory patients.

Procedure. The test is carried out by having the subject finish his usual supper by 6 P.M. He then has nothing to eat or drink until noon the following day; he may carry on ordinary activity during this time. Urine specimens are collected at 8 A.M., 10 A.M., and 12 NOON, with complete emptying of the bladder each time. The specific gravity of each specimen is then determined, with the urine at room temperature and with an ordinary urinometer which has been checked with distilled water.

The most concentrated specimen is tested for the presence of protein, and if present its amount is quantitatively determined in order to correct the specific gravity when necessary. For every 1% of protein present in the urine, 0.003 is subtracted from the observed specific gravity; any proteinuria less than 0.3% does not need to be considered. Thus the specific gravity of most urines will not require correction.

We have further simplified the easy and accurate method of Lashmet and Newburgh³ for quantitative measurement of proteinuria:

Method.* To 1 cc. of urine add 9 cc. of distilled water, making a 1:10 dilution. Add the diluted urine to the U mark of Tube 1 and then add 2% sulfosalicylic acid up to the R mark. Mix thoroughly, and allow to stand for 3 minutes. If the resulting turbidity matches that of the *standard tube*, the urine contains 0.3% protein; the specific gravity of the urine is then corrected by subtracting 0.001. If the turbidity is less than that of the standard tube, no correction of the observed specific gravity is necessary.

If the turbidity of Tube 1 is greater than that of the standard tube, add the 1:10 diluted urine to the U mark of Tube 2, and then add 2% sulfosalicylic acid to the R mark. Mix thoroughly and allow to stand; if the turbidity matches that of the standard tube, the urine contains 0.6% protein. The observed specific gravity then is corrected by subtracting 0.002. If the turbidity is greater than that of the standard, add the diluted urine to the U mark of Tube 3, and sulfosalicylic acid to the R mark. If the turbidity resulting in Tube 3 matches that of the standard tube, the urine contains 1% protein. The observed specific gravity is then corrected by subtracting 0.003. Urine containing more than 1% protein should be diluted 1:20, and the foregoing procedure with the 3 tubes is repeated.

The 2% sulfosalicylic acid reagent may turn pink on standing. Such solutions should be discarded, for the pink cast interferes in accurate comparison with the standard.

Preparation of the standard turbidity suspension: A stock suspension is first prepared. To 200 cc. of distilled water in a 500 cc. volumetric flask, add 50 cc. of 0.1 normal

* A set of calibrated tubes, standard tube, and a support (A21-195) may be obtained from Eberbach & Son, Co., Ann Arbor, Mich.

sodium hydroxide solution and 8 gm. of copper sulfate (hydrous). Then add distilled water to 500 cc. Shake the stock suspension vigorously to insure uniform turbidity. Exactly 2 cc. of this mixture is transferred by pipette to a test-tube, and 23 cc. of distilled water is added. This is the standard tube, and it can be made permanent by drawing out its open end and sealing in a flame. Before using, the standard tube should be inverted several times to obtain uniform turbidity.

maximum specific gravity of 1.025 or higher, and 2 subjects concentrated to 1.024. We thus have placed a maximum specific gravity of 1.025 as the lower limit of normal for this 18 hour renal concentration test.

A single determination was done on each of the 40 normals except 1. The latter concentrated only to a specific gravity of 1.020 on his first determination, but on his second test the maximum spe-

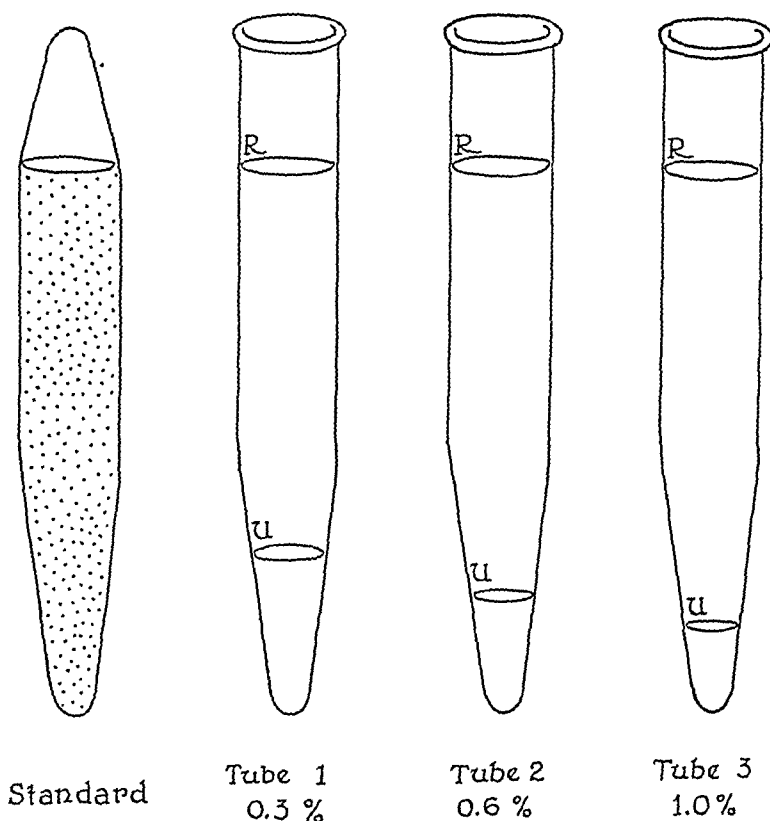


FIG. 1.—Set of tubes for rapid quantitative determination of proteinuria.

Tube 1:

U mark is at 1.66 cc. = 0.3% protein.

Tube 2:

U mark is at 0.83 cc. = 0.6% protein.

Tube 3:

U mark is at 0.5 cc. = 1.0% protein.

The R mark is at 12.5 cc.

cific gravity was 1.025. It is thus recommended that a single low determination not be accepted as evidence of impaired renal function, and that the test be repeated before such a conclusion is reached.

It is realized that normal kidneys may concentrate to a higher specific gravity when the test is carried out over a longer period of time. The value of 1.029 is the lower limit of normal for the 38 hour concentration test of Lashmet and Newburgh. But it is felt that by the end of 18 hours

Results. This test was performed on 40 normal medical students who showed no evidence of renal disease. The urinalysis on each subject was entirely negative. Of the subjects, 38 concentrated to a

TABLE 1.—THE MAXIMUM SPECIFIC GRAVITY OF 40 NORMAL SUBJECTS

Maximum specific gravity	No. subjects	Maximum specific gravity	No. subjects
1.024	2	1.030	4
1.025	6	1.031	4
1.026	8	1.032	3
1.027	4	1.035	1
1.028	4	1.040	1
1.029	3		

TABLE 2.—INTERPRETATION OF MAXIMUM SPECIFIC GRAVITY VALUES IN THE 38 HOUR AND 18 HOUR CONCENTRATION TESTS

Kidney function	Maximum specific gravity	
	38 hour test	18 hour test
Normal	1.029 and higher	1.025 and higher
Borderline	1.027-1.028	1.024
Slight impairment	1.022-1.026	1.020-1.023
Moderate impairment	1.016-1.021	1.015-1.019
Marked impairment	1.015 and below	1.014 and below

TABLE 3.—COMPARISON OF RESULTS OF 38 HOUR AND 18 HOUR CONCENTRATION TESTS IN 100 PATIENTS WITH HYPERTENSIVE DISEASE (FAILURE OF CORRELATION IN 11 CASES)

Case No.	38 hr. test	18 hr. test	Correlation	Case No.	38 hr. test	18 hr. test	Correlation
1	1.023	1.021	+	51	1.030	1.024	+
2	1.027	1.024	+	52	1.025	1.025	+
3	1.030	1.024	+	53	1.031	1.026	+
4	1.028	1.026	+	54	1.025	1.016	0
5	1.028	1.024	+	55	1.025	1.023	+
6	1.018	1.014	0	56	1.029	1.026	+
7	1.033	1.029	+	57	1.030	1.017	0
8	1.028	1.024	+	58	1.028	1.025	+
9	1.021	1.017	+	59	1.024	1.025	+
10	1.024	1.022	+	60	1.026	1.027	+
11	1.016	1.013	+	61	1.024	1.022	+
12	1.015	1.014	+	62	1.025	1.023	+
13	1.010	1.013	+	63	1.028	1.026	+
14	1.023	1.019	0	64	1.021	1.026	+
15	1.028	1.026	+	65	1.029	1.024	+
16	1.021	1.020	+	66	1.028	1.017	0
17	1.022	1.020	+	67	1.026	1.023	+
18	1.023	1.020	+	68	1.030	1.028	+
19	1.026	1.024	+	69	1.031	1.028	+
20	1.026	1.023	+	70	1.026	1.022	+
21	1.020	1.018	+	71	1.024	1.020	+
22	1.027	1.024	+	72	1.023	1.022	+
23	1.024	1.023	+	73	1.027	1.024	+
24	1.029	1.024	+	74	1.028	1.012	0
25	1.032	1.031	+	75	1.026	1.021	+
26	1.031	1.025	+	76	1.023	1.026	+
27	1.024	1.018	0	77	1.024	1.025	+
28	1.025	1.020	+	78	1.022	1.020	+
29	1.032	1.020	0	79	1.029	1.024	+
30	1.030	1.027	+	80	1.025	1.021	+
31	1.028	1.024	+	81	1.024	1.025	+
32	1.022	1.021	+	82	1.029	1.027	+
33	1.025	1.023	+	83	1.029	1.020	0
34	1.028	1.025	+	84	1.028	1.024	+
35	1.028	1.025	+	85	1.023	1.022	+
36	1.028	1.024	+	86	1.031	1.026	+
37	1.024	1.022	+	87	1.028	1.027	+
38	1.026	1.027	+	88	1.024	1.023	+
39	1.024	1.020	+	89	1.027	1.026	+
40	1.028	1.024	+	90	1.022	1.023	+
41	1.028	1.026	+	91	1.017	1.025	+
42	1.026	1.023	+	92	1.032	1.031	+
43	1.026	1.024	+	93	1.019	1.017	+
44	1.026	1.027	+	94	1.025	1.020	+
45	1.015	1.012	+	95	1.012	1.012	+
46	1.024	1.020	+	96	1.025	1.021	+
47	1.034	1.026	+	97	1.030	1.024	+
48	1.032	1.020	0	98	1.028	1.026	+
49	1.032	1.027	+	99	1.026	1.015	0
50	1.029	1.025	+	100	1.027	1.025	+

the kidneys have been subjected to a strain sufficient to enable an adequate differentiation of the normal from the abnormal.

In order to determine whether the 18 hour test is as effective a measure of kidney function as the 38 hour test, a comparison of results was made in 100 cases of hypertensive disease on whom both the 38 hour and the 18 hour tests had been performed. The shorter test was done when these patients returned 1 year later for studies. There was failure of correlation of the results in only 11 of the 100 cases; thus the 18 hour test is sufficiently accurate to warrant its use. The disparity of the results of the 2 tests in these 11 cases may be partly accounted for by the possible increase of impairment of kidney function occurring during the year intervening between the 2 tests, for each of these patients had hypertensive disease. Also, only a single determination was done in each case even when the result was abnormal.

Of 200 cases of essential hypertension, 124 cases (62%) showed impaired concentrating ability.¹ Each of these patients had hypertensive disease of sufficient severity to warrant hospitalization for surgical treatment of the hypertension;

the elevated blood pressure was not a coincidental finding. The concentration test was found to be more sensitive than the urea clearance test in detecting early kidney damage in essential hypertension. It was also found that it is unnecessary to measure the urea clearance when the concentrating ability is normal.

Each of 8 cases of glomerulonephritis, both subacute and chronic, showed impaired concentrating ability. The maximum specific gravity in these cases ranged from 1.010 to 1.020.

Summary. An 18 hour concentration test of kidney function is presented. It is easily performed, and it is particularly suitable for use on ambulatory patients. Under the conditions of this test, normal kidneys concentrate urine to a specific gravity of 1.025 and higher, while diseased kidneys do not.

A simple, rapid, and accurate method for quantitative determination of proteinuria is also presented. It is based on the comparison of the turbidity of urine in which protein has been precipitated by 2% sulfosalicylic acid, with the turbidity of a permanent, standard suspension of inorganic substance.

REFERENCES

1. ISBERG, E. M., and BARKER, P. S.: Kidney Function in Essential Hypertension, *J. Michigan State Med. Soc.*, 44, 817, 1945.
2. LASHMET, F. H., and NEWBURGH, L. H.: An Improved Concentration Test of Renal Function, *J. Am. Med. Assn.*, 99, 1936, 1932.
3. LASHMET, F. H., and NEWBURGH, L. H.: An Improved Concentration Test of Renal Function: IIA. Simple Method for Measuring Proteinuria, *J. Am. Med. Assn.*, 100, 1328, 1933.

THE RELATIONSHIP BETWEEN PACKED RED CELL VOLUMES AND LYMPHOCYTE COUNTS

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A RELATIONSHIP between cell pack (hematocrit) values and the percentage of lymphocytes found in the differential count has recently been demonstrated by Jung, Hepler and Maynard.¹ In the course of blood investigations on 35 students they noticed that subjects with low cell pack volumes tended to have high lymphocyte percentages and *vice versa*. Hematologic data from 160 dispensary patients disclosed the same relationship, especially in those patients with cell pack volumes above 38 cc. per 100 cc. of blood. Jung, Hepler and Maynard¹ think that their finding may be evidence of a reciprocal relationship between lymphocyte production and erythrocyte production, or alternatively that it may be due to periodic increases in the discharge of lymph from the thoracic duct into the veins, so that from time to time in the normal body there is hemodilution accompanied by a release of lymphocytes into the blood stream.

However, these changes in lymphocyte percentage do not necessarily indicate that the number of lymphocytes per c.mm. of blood has altered: the percentage of lymphocytes in the differential count may be high because there are many lymphocytes in circulation or because there are few granulocytes. It may well be that the reciprocal relationship between lymphocyte percentage and cell pack volume found by Jung, Hepler and Maynard¹ is really due to changes occurring in the

granulocytes at different cell pack values. The point can readily be settled by finding the absolute number of granulocytes and lymphocytes per c.mm. which correspond to different cell pack volumes; if there is any true relationship between cell pack volume and lymphocyte production or release, then it should still be demonstrable in the absolute lymphocyte count.* We have examined 100 subjects with this point in view.

Material and Methods. *Subjects.* One hundred males with cell pack volumes above 38 cc. per 100 cc. of blood (the range in which the association with lymphocyte percentage is most evident¹) were used. They were either healthy people or had some local lesion which would be unlikely to affect the blood picture (non-syphilitic mental observation cases, and so forth). Their ages ranged from 16 to 61 years.

Blood Samples. These were collected between 7.30 and 10 A.M. with the subject fasting. Five cc. of blood were taken by venepuncture with the minimum of venous stasis and transferred to a tube containing a suitable quantity of Wintrobe's² oxalate mixture. This venous sample was used for cell pack determination, white cell count and differential count.

Cell Pack Determination. The blood was spun in Wintrobe tubes for 30 minutes in an International centrifuge (head No. 240) at 3000 revolutions per minute; the speed was checked by tachometer.

White Cell Count. Dilutions were made using 5 cc. of white cell fluid and 0.2 cc. of

* We believe that the authors' point is well taken; absolute numbers are usually of more value than percentages. However, it should be realized in this case that the direct estimations are of the total numbers of leukocytes and percentages. The absolute values, being computed from the two figures, each of which may have considerable range of error, might be even further from actuality.—EDITORS.

blood; 9 fields of 1 sq. mm. each were counted in the hemacytometer chamber.

Differential Count. Immediately after removing the venous sample, coverslip films were made from a fixed quantity of blood. The films were stained by Leishman's stain and 300 cells were differentiated by an observer who was unaware of the other data in the investigation. Smear cells and degenerate forms were found to be distributed without relation to the cell pack volume and were ignored in the calculation of the differential count.

pretation of the results is statistically sound.

Thus, the relationship between cell pack volumes and lymphocyte percentages does not indicate any real change in the number of lymphocytes in circulation, but is due to an increase in the number of granulocytes in circulation as the cell pack volume rises. Presumably the well-known diminution of granulocytes in many types of anemia and their increase in polycythemia vera are extreme instances of this

TABLE 1.—RELATION OF GRANULOCYTES AND LYMPHOCYTES TO CELL PACK VOLUME

Cell pack volumes (cc. per 100 cc. blood)	No. in group	Total leukocytes (per c.mm.)	Granulocytes		Lymphocytes	
			%	Per c.mm.	%	Per c.mm.
39-44.5 . . .	25	7148	63.26	4610	33.28	2305
45-47.5 . . .	49	7570	65.26	4934	30.59	2320
48-56.5 . . .	26	9390	68.12	6422	27.98	2549

TABLE 2.—CORRELATION COEFFICIENTS

Hematocrit value and total leukocytes per c.mm.	=	+0.319 ± 0.090*
Hematocrit value and granulocytes, %	=	+0.271 ± 0.093*
Hematocrit value and granulocytes per c.mm.	=	+0.347 ± 0.088*
Hematocrit value and lymphocytes, %	=	-0.242 ± 0.094*
Hematocrit value and lymphocytes per c.mm.	=	+0.062 ± 0.100

The regression lines do not differ significantly from linearity.

* Statistically significant association.

Results. Table 1 shows the general relationships. As the cell pack volume rises, the total white cell count per c.mm. increases. This is almost entirely due to an increase in the number of granulocytes per c.mm.; the percentage of granulocytes is consequently increased and the percentage of lymphocytes reduced. There is no significant change in the number of lymphocytes per c.mm. at different cell pack levels. Table 2 indicates that this inter-

association between the number of granulocytes and erythrocytes in circulation.

Summary. The negative correlation between cell pack volumes and lymphocyte percentages has been confirmed. This effect is secondary to changes occurring in the percentage and absolute count of granulocytes. There is no significant change in the absolute lymphocyte count at different cell pack levels within the range studied.

REFERENCES

1. JUNG, F. T., HEPLER, O. E., and MAYNARD, M. S.: *AM. J. MED. SCI.*, 209, 336, 1945.
2. WINTROBE, M. M.: *Clinical Hematology*, London, Kimpton, p. 200, 1942.

THE SEDIMENTATION RATE AS AN AID IN THE DIAGNOSIS OF ACUTE POLIOMYELITIS

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FROM July to November 1945, there have been 223 cases of poliomyelitis interned at the South View Hospital of the Milwaukee Health Department. During that time more than 100 cases have been sent to the Hospital as suspected poliomyelitis. During this 4 month period we have had 420 consultation calls in the city. Frank cases of this disease were diagnosed quite readily, by the attending physicians. However, the borderline cases and the abortive types caused considerable difficulty in diagnosis. This necessarily meant that the suspected poliomyelitis case was sent to the hospital for a spinal fluid examination and observation. Attending physicians occasionally are hesitant in sponsoring a spinal puncture as family objections may provoke delay in carrying out this laboratory aid. There is still a small amount of skepticism on the part of the laity to subscribe to spinal puncture and oftentimes this comment is made: "We don't want the child to have a brain tap." In the past, under these circumstances, we were dependent upon the clinical course of the disease and, therefore, a small proportion of cases had undetermined diagnoses.

The sedimentation rate aided in ruling out uncomplicated virus diseases from those of bacterial origin and has been a constant comfort in the approach to the diagnosis where spinal punctures were refused. Recently Rosin¹ called attention to the marked variability in the sedimentation rate and white blood count in poliomyelitis.

Method of Determination. The Westergren method of sedimentation rates was used, the normals for this method being 0 to 15 mm. for males and 0 to 20 mm. for

females in the 1st hour. Two determinations were done on each patient. 0.2 cc. of a 3.8% sodium citrate plus 1.8 cc. of blood were used. The first sedimentation rate was performed between the 2nd and 20th day from the onset of the illness, while the second was done from the 7th to the 30th day from the beginning of the disease. The average duration of time between the 2 determinations was 7.8 days.

Results of Sedimentation Rate Determinations. Among the first 100 cases we determined sedimentation rates on 76 as noted in Table 1. The rates in uncomplicated cases were practically all normal on entrance and also after the end of 1 week. Of the 5 bulbar types, including those *in extremis*, 3 had a normal rate. Of the 32 spinal types, only 5 presented a slight elevation of the rate, 1 of which had a slight elevation after the 1st week. In 14 of the 39 non-paralytic poliomyelitis cases there was an elevation of the rate on one or both examinations. It can readily be noted that there was no appreciable difference in the rates on the first or second examinations.

In this series of 76 cases, only 21 showed an increase in either or both determinations and 11 of these had elevations of from 1 to 4 mm.—a negligible increase. The remaining 10 cases had elevated rates from 5 to 25 mm. above the normal value, and 4 of these cases had concurrent disorders to account for the high elevation.

CASE 1. A 56 year old female whose death occurred 24 hours after the second test was done. The second test showed an elevation of 7 mm. above the normal, and this could be explained by the fact that at autopsy pulmonary infarctions were found due to congestive heart failure.

CASE 2. A 5 year old girl. The first specimen was 24 mm. above the normal and the second 6 mm. Her spinal fluid showed 400 cells per c.mm., 81% of which were polymorphonuclear cells. In addition to poliomyelitis, a marked rhinopharyngitis was present.

CASE 3. A 12 year old boy; bulbar type. A marked cervical adenitis was noted, due to a superimposed bacterial infection. This accounted for the elevation of 15 mm. in the first specimen and 8 mm. in the second.

TABLE 1.—SEDIMENTATION RATES IN 152 CASES

No. cases	Normal rate (both samples)	Elevated rate (both samples)	Elevated to normal rate	Normal to elevated rate
Bulbar—5	3 (60%)	2 (40%)	0 (0%)	0 (0%)
Paralytic—32	27 (84.3%)	2 (6.3%)	1 (3.1%)	2 (6.3%)
Non-paralytic—39	25 (64.1%)	6 (15.4%)	8 (20.5%)	0 (0%)
Total—76	55 (72.4%)	10 (13.1%)	9 (11.8%)	2 (2.6%)

TABLE 2.—AVERAGE RISE IN 21 CASES WITH INCREASED SEDIMENTATION RATE

Paralytic		Non-paralytic		Bulbar	
First	Second	First	Second	First	Second
1.6 mm.	6.0 mm.	8.7 mm.	1.0 mm.	11.5 mm.	4.5 mm.

CASE 4. A 5 year old girl; paralytic type. The first specimen had a normal rate, while the second had an elevation of 15 mm. However, the second sedimentation rate was done only 18 hours before she expired, so that the patient was, at that time, *in extremis* with pulmonary involvement.

Thus there were only 6 cases in the whole series in which an increased sedimentation rate could not be explained.

White Blood and Spinal Fluid Counts.

The white blood counts of all cases varied between 3000 and 16,000. At no time was there a marked polymorphonuclear leukocytosis in the differential picture. The uniformity of the sedimentation rates was not influenced by the slight leukopenia nor the slight leukocytosis. Our records reveal variable spinal fluid cell counts of 18 to 650 white blood cells per c.mm. There was no appreciable relationship between the white blood count and the spinal fluid cell count.

Discussion. Although it is apparent that the sedimentation rate is not pathognomonic in the diagnosis of poliomyelitis, yet it is not erroneous to state that the sedimentation rate is quite constantly within normal range. It has proved of

extreme value in aiding us in the differential diagnosis.

The following illustrated cases, referred to the Health Department, had fast sedimentation rates which indicated the need of further investigation for proper diagnosis.

CASE 5. A 19 year old boy who complained of headache, nausea, and pain in the neck for 2 days. Poliomyelitis was suspected but ruled out on the basis of a 48 mm.

sedimentation rate. The case was later diagnosed as a streptococcic infection of the mesopharynx.

CASE 6. A boy 7 years old who complained of pain in his right knee and calf muscles. His temperature varied from 99.6° to 101° F. A sedimentation rate of 45 mm. was an aid in excluding poliomyelitis. The case proved to be rheumatic fever.

CASE 7. A 2 year old boy who complained of pain in the left heel on pressure. Six weeks previously his foot had been struck. Subsequent to this he began to develop a limp, though there were no external signs of injury. He also complained of weakness in the right forearm. The sedimentation rate of 96 mm. excluded poliomyelitis from the diagnosis. Roentgen rays and further investigation revealed osteomyelitis of the left acetabulum.

Conclusion. 1. It is apparent from our experience that the uncomplicated disease poliomyelitis is represented by a fairly constant, normal sedimentation rate.

2. The sedimentation rate is an aid in the differential diagnosis of poliomyelitis from the bacterial diseases.

3. There is no correlation between the white blood count, spinal fluid cell count, and the sedimentation rate.

REFERENCE

1. ROSIN, W., FRANK, W. P., and HAMILTON, P. M.: The Sedimentation Rate and White Blood Count in Acute Poliomyelitis, *J. Pediat.*, 24, 679, 1944.

THE EPIDEMIOLOGIC SIGNIFICANCE OF AMPLITUDES OF SEASONAL FLUCTUATION IN INFECTIOUS DISEASES

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SEASONAL prevalence, one of the most constant characteristics of infectious diseases, has been generally attributed to the operation of some single factor—the favored one being seasonal variation in the mechanism by which the infectious agent is transmitted. But, so far, the exact reasons for the seasonal fluctuation observed in many diseases have not been clearly established.

In an earlier report in this Journal of seasonal variation in a number of infectious diseases,^{2,6} certain differences in amplitudes of seasonal fluctuation were noted, which, in general, appeared to be characteristic of certain classes of disease.

“As judged from the magnitude of seasonal variations in infectious disease, in harborage of certain infectious agents and in physiologic functions, it is anticipated that the host-parasite interaction may be affected by season in two distinct ways. Seasonal changes in the host may have the simple effect of producing a seasonal variation in resistance to disease while not necessarily affecting the harborage or transmission of the infectious agent. On the other hand, both resistance to disease and resistance to infection (multiplication of the virus which in turn affects transmission) may be influenced by season. . . . Differences in the magnitude of seasonal variation in a number of infectious diseases affords some indication that the former may be a general rule in bacterial infection, and the latter in virus infections—a point, however, which will require further investigation.”² The purpose of the present study

is the further analysis of amplitudes of seasonal variation in a number of infectious diseases.

As has been discussed previously,² there is a wide divergence among the seasonal curves of the common upper respiratory diseases in the same geographic area with respect to time of peak incidence, with marked differences between northern and southern states. Because of this northern-southern variation, and because of certain exceptions in one or the other locality, data from 2 northern states, Massachusetts and Connecticut, as well as from 2 southern states, Alabama and Mississippi, have been considered in this study. The respective total populations of these combinations are roughly comparable.

The annual percentage distribution of cases by months of the epidemic years (the 12 month period beginning with the month of lowest incidence) for each of the common upper respiratory diseases was averaged over a period of 14 epidemic years covering the period 1925–1939.⁶ By this method, years of high and low incidence are given equal weight in the final mean percentage distribution. Since a single year of very high incidence could alter the shape of the curve of seasonal distribution for an entire period,¹ curves of the seasonal distribution of cases in years of high, low, and intermediate incidence were compared. These comparisons indicated that the shape of the curves used in this study were not the reflection of excessively high or low years, but, in general, were characteristic of the various diseases throughout the period.

In order to facilitate comparison of amplitudes of seasonal variation alone, without regard to differences in the periods or phases in the seasonal curves of the different diseases, the mean annual percentage distribution curves all have been set forward or back the number of months required to make their periods and phases coincide.

in both the northern and southern states (Charts 1 and 2). Furthermore, as judged by the amplitude of seasonal variation, all upper respiratory diseases can be classified under 3 types of seasonal curves: 1 type of curve with low amplitude composed entirely of diseases of bacterial etiology; a 2nd of intermediate amplitude composed of 2 bacterial diseases and a single

TABLE 1.—DISEASES GROUPED ACCORDING TO AMPLITUDE OF SEASONAL VARIATION

ETIOLOGY	AMPLITUDE		
	Low	INTERMEDIATE	HIGH
Upper Respiratory			
Bacterial *	Meningitis, Mass.-Conn. (Aug.-July) Meningitis, Ala.-Miss. (July-June) Whooping Cough, Mass.-Conn. (June-May) Whooping Cough, Ala.-Miss. (Aug.-July) Diphtheria, Mass.-Conn. (May-April)	Diphtheria, Ala.-Miss. (March-Feb.) Scarlet Fever, Mass.-Conn. (June-May) Scarlet Fever, Ala.-Miss. (March-Feb.) Poliomyelitis, Ala.-Miss. (Dec.-Nov.)	Poliomyelitis, Mass.-Conn. (Jan.-Dec.) Mumps, Mass.-Conn. (July-June) Mumps, Ala.-Miss. (July-June) Measles, Mass.-Conn. (Aug.-July) Measles, Ala.-Miss. (Aug.-July) Chicken-pox, Mass.-Conn. (June-May) Chicken-pox, Ala.-Miss. (June-May)
Upper Respiratory Virus			
Intermediary Transmission Group	Typhoid Fever, Mass.-Conn. (Nov.-Oct.) Typhoid Fever, Ala.-Miss. (Nov.-Oct.) Typhus Fever, Reg. Area (Jan.-Dec.) Malaria, Reg. Area (Jan.-Dec.)		

* Smallpox in the U. S. Registration Area conforms with this group.

In Table 1, the diseases considered are listed according to amplitudes of seasonal fluctuation, low, intermediate or high, and the months of setback used to make their periods and phases coincide in the graphs to follow are indicated.

On the basis of differences in the amplitude of seasonal variation, upper respiratory diseases, with certain exceptions to be discussed later, can be separated into 2 groups, 1 of bacterial, the other of virus etiology. The exceptions, as noted in Table 1, were diphtheria and poliomyelitis in the southern states, and scarlet fever virus disease (Chart 2); and a 3rd of high amplitude composed entirely of diseases of virus etiology. As can be seen in Charts 1 and 2, there is little difference in amplitude between curves for the respective diseases in northern and southern states, except diphtheria and poliomyelitis. Further selected comparisons indicated that the differences in amplitude between upper respiratory diseases of bacterial and virus etiology shown here were the same when data from the U. S. Registration Area^s were used. Also, in Chart 2, the data on certain diseases of in-

intermediary transmission are treated in the same manner. The amplitude of the seasonal curves of this group of diseases is of the same order as that of the bacterial and virus upper respiratory diseases comprising the intermediate curve of the upper respiratory group.

In order to facilitate further analysis, the mean of each of the 4 groups of curves was determined. A comparison of the means of the bacterial and virus upper respiratory diseases (Chart 3) reveals the striking differ-

ence in amplitude, the ratio of low to high for the virus group (1:9.7) being more than 4 times that of the bacterial group (1:2). The rate of increase of the mean bacterial upper respiratory curve follows an arithmetic progression, suggesting simple numerical variation. The mean curve of the intermediary transmission group, as would be expected in phenomena conforming to the laws of mass action, exhibits a geometric increase. Similarly, the rate of increase of the mean virus upper respiratory curve also is more nearly geometric.

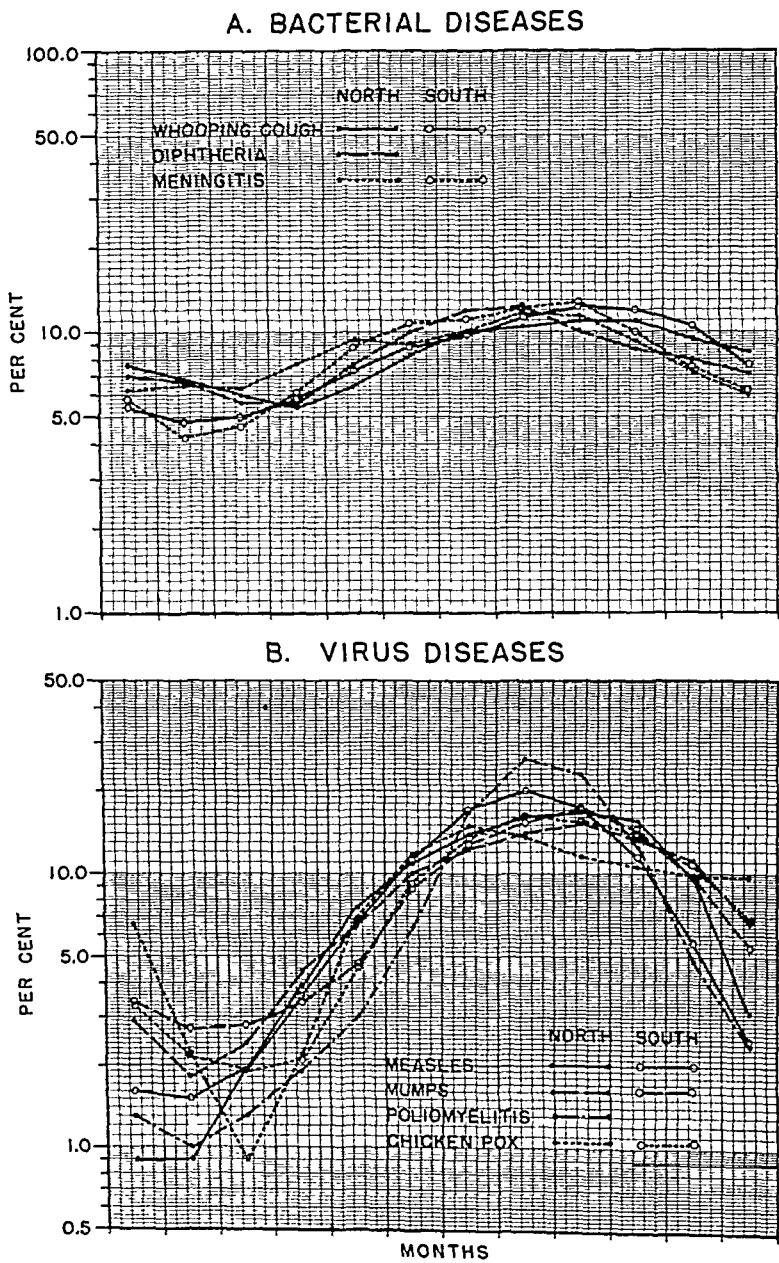


CHART 1

When the relative incidence of a disease, or a group of diseases, is plotted logarithmically against time the curve fits the equation:

$$\text{Log } D_1 = A + a \sin x$$

Then, if the relative incidence of a second disease or group of diseases with the same period and phase, but with a larger amplitude due to a simultaneous variation is plotted; the curve fits the equation:

$$\text{Log } D_2 = B + b \sin x$$

Then the receptivity function of the 2 curves is:

$$\frac{D_2}{D_1} = \frac{e(B + b \sin x)}{e(A + a \sin x)}$$

or,

$$\frac{D_2}{D_1} = e[(B - A) + (b - a) \sin x]$$

The logarithm of this function is the exponent of the Napierian base, which represents the difference of the 2 curves as plotted on

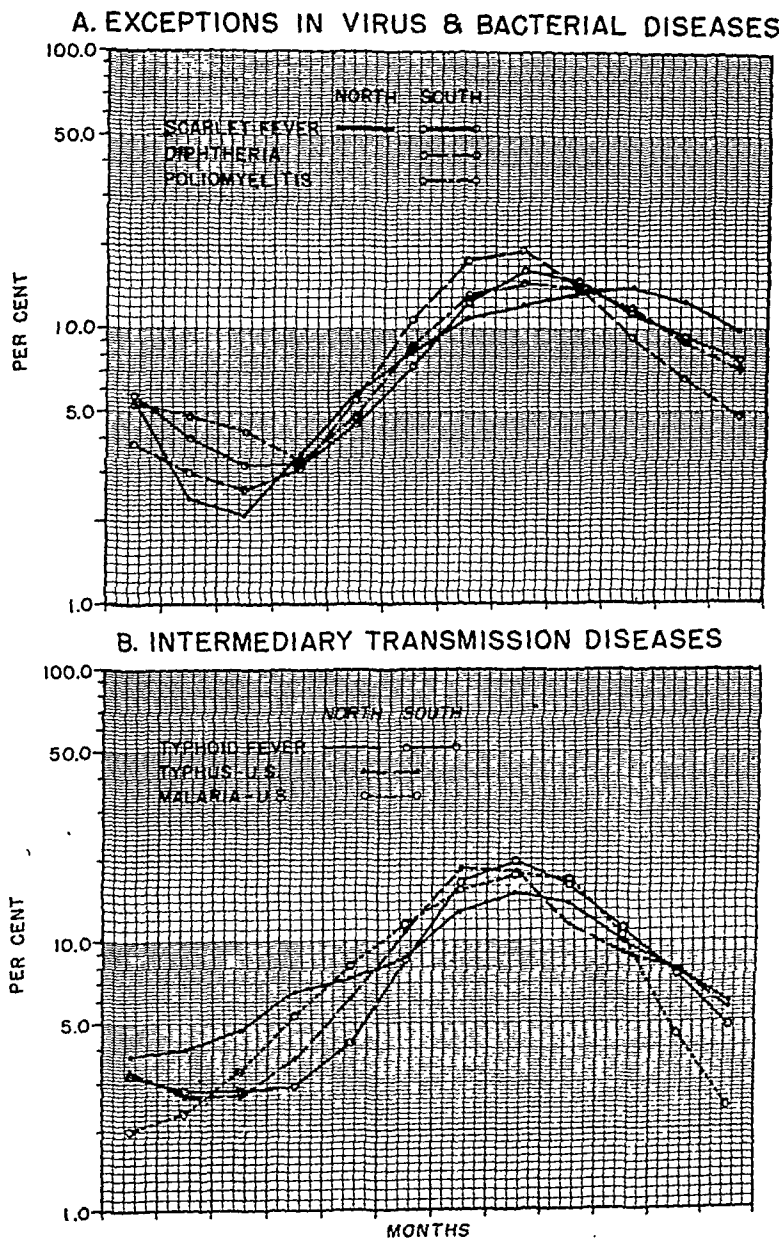


CHART 2-

logarithmic paper. The amplitude of this difference can be determined by measuring the differences at the corresponding points on the 2 curves.

More simply, if the mean bacterial curve is subtracted logarithmically from the mean virus curve, the differences totalled and re-percented, the resulting curve represents the difference in amplitude between the mean bacterial and virus curves. The difference in amplitude between the mean bacterial and mean virus

curves is almost identical with the mean curves for the intermediate group of upper respiratory diseases, and the group of diseases where transmission is intermediary as well (Chart 3). In other words, the amplitude of the mean virus curve is equal to the combined amplitudes of the bacterial upper respiratory and intermediary transmission groups of diseases.

The lack of knowledge as to the frequency and extent of virus harborage in most diseases of viral etiology precludes

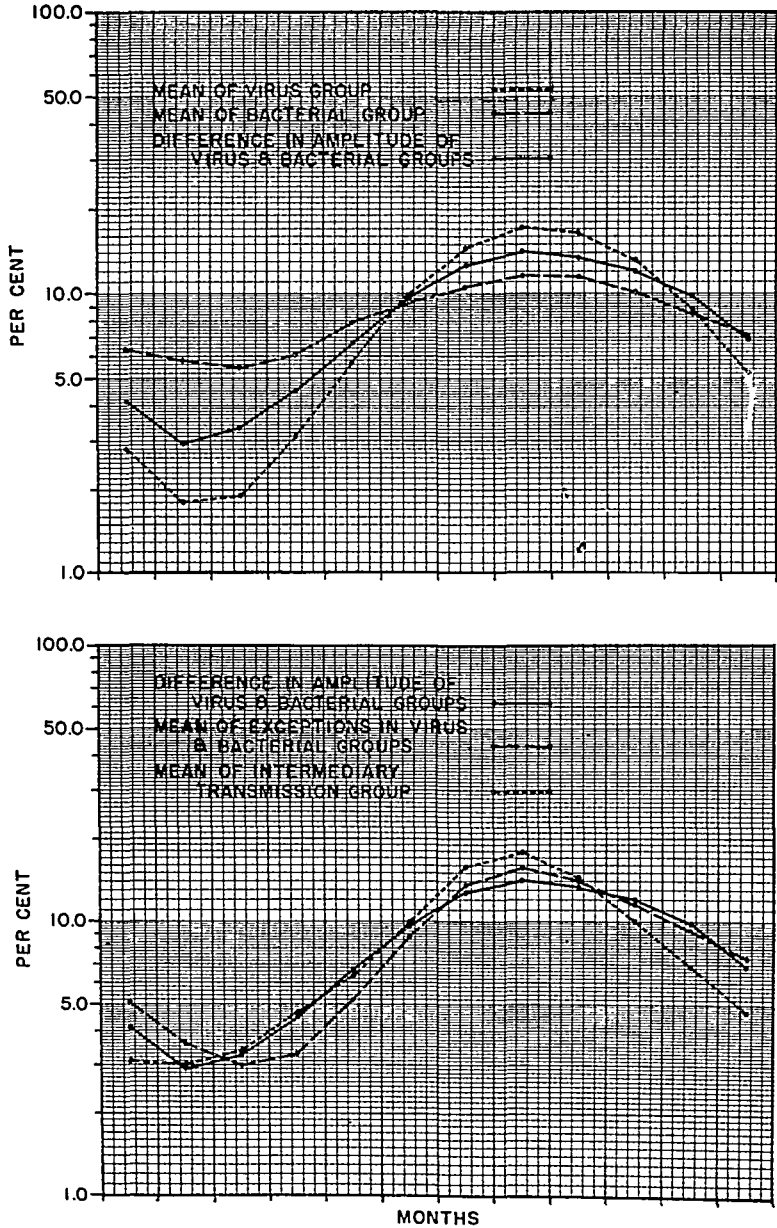


CHART 3

any discussion as to the stability of the dissemination rate of virus infection through healthy carriers, or perhaps more strictly in the case of virus infection, through sub-clinical infection.

However, data are available which indicate that the incidence of bacterial upper respiratory disease varies with season in spite of little or no seasonal fluctuation in the incidence of healthy carriage of the respective microorganisms. Meningococcus meningitis, for example, exhibits the

amplitude of seasonal variation characteristic of the group of bacterial diseases in the face of no corresponding fluctuation in the meningococcus carrier rate. In other words, the attack rate in meningococcus carriers follows a seasonal variation of the same amplitude as that of the incidence of meningococcus meningitis, which is that of the bacterial upper respiratory diseases as a group⁷ (Chart 4). It therefore appears that seasonal variation in meningitis may be determined by the

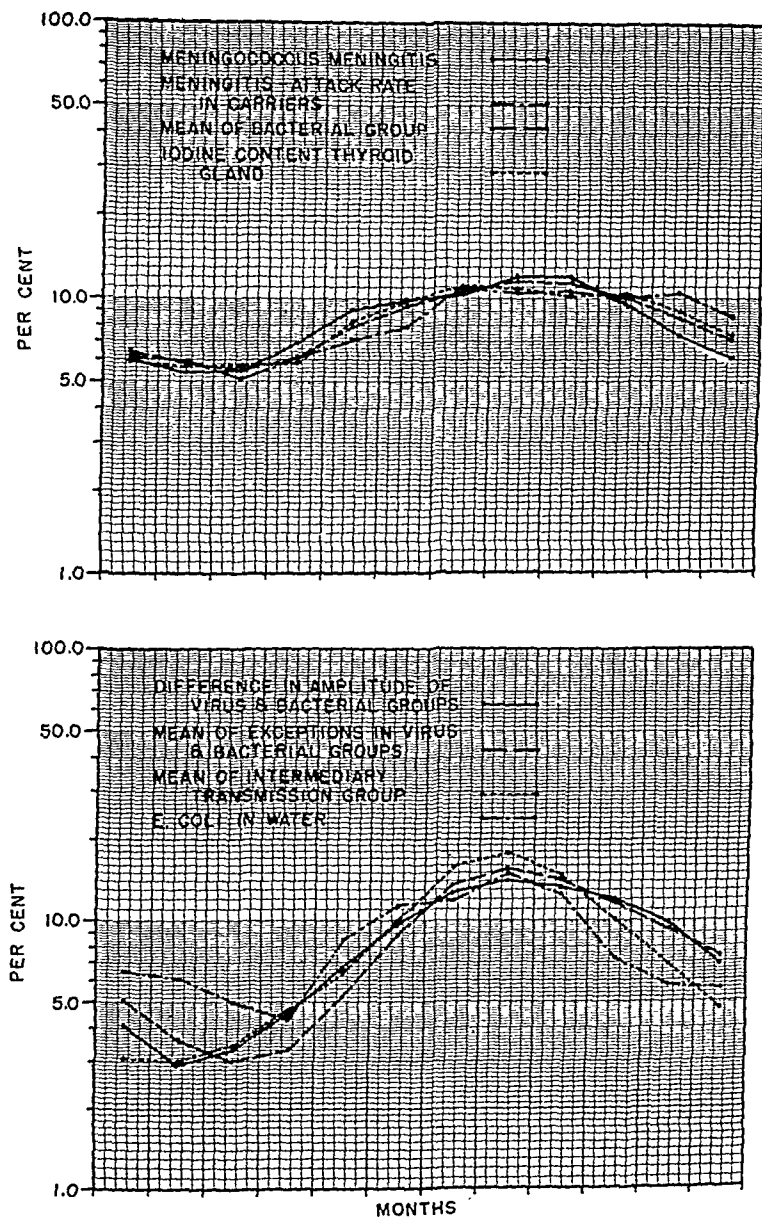


CHART 4

operation of the single factor of seasonal variation in susceptibility to the clinical disease.

In this connection it might be pointed out that the amplitude of a number of seasonal variations in physiologic processes is of the same order as that of seasonal variation in the bacterial group of infections. For comparison, the seasonal variation in the iodine content of the thyroid gland⁴ is included in Chart 4.

In the intermediary transmission group of diseases (typhus and malaria, for example), on the other hand, seasonal variation is generally considered to be determined primarily by the bionomics of the

transmission for these diseases. In the case of the diseases propagated by intermediary transmission, seasonal variation would appear to be due to fluctuation in the extra-human virus reservoir. A similar seasonal variation in a human virus reservoir would be expected to exhibit the same geometric amplitude of seasonal variation.

Since the amplitude of seasonal variation in the virus group of upper respiratory diseases is equal to the combined amplitudes of seasonal variation in the bacterial group (attributed to variation in susceptibility alone) and that of the intermediary transmission group (attributed to varia-

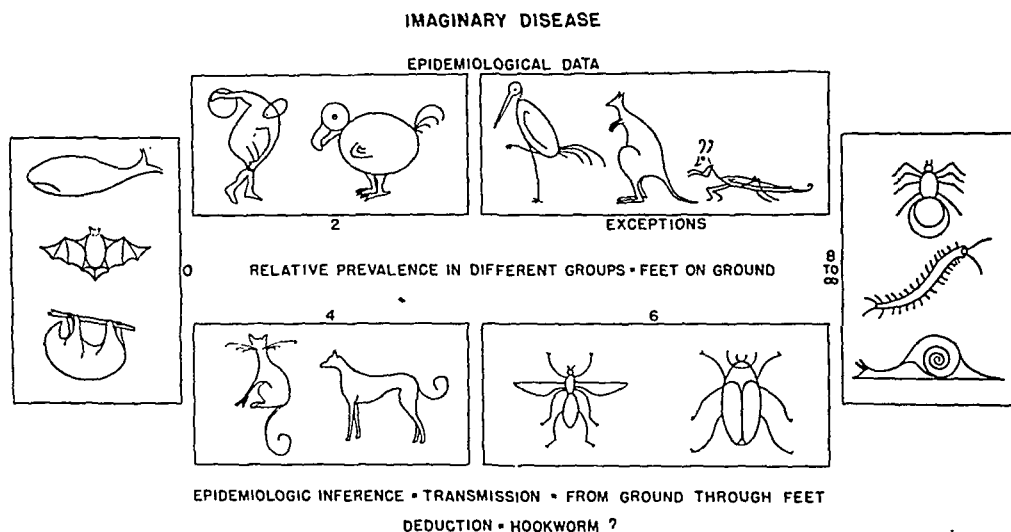


CHART 5—Illustrating the relative prevalence in an imaginary disease that occurs in 3 main groups in proportion to the number of legs of each individual of each group.

vector rather than seasonal variations in the host. Typhoid fever is included in this group since its seasonal variation is generally considered to be the result of seasonal variations in opportunities for transmission. That this may be so is suggested, for example, by the seasonal variations of *E. coli* in water samples collected at various distances from the source of pollution in the Illinois River⁵ (Chart 4).

The fact that diphtheria and poliomyelitis in warmer climates, and scarlet fever in both warm and cool climates have amplitudes of seasonal fluctuation of the same order as that of the intermediary group, in no sense infers intermediary

tion in virus reservoir), seasonal fluctuation in the virus upper respiratory group would appear to be the result of combined activity of the 2 factors—variation in susceptibility and variation in the human virus reservoir.

The explanation for the exceptions to the rule which applies in general in the amplitude of seasonal fluctuation in virus and bacterial diseases transmitted by direct contact is not clear. However, the diseases in which exceptions occur differ in certain respects from the groups to which they belong, and it is conjectured that the exceptions in amplitude of sea-

sonal fluctuation in them may in some way be accounted for by these differences.

In bacterial diseases where the rule is a seasonal fluctuation of low amplitude, it is inferred that a simple seasonal variation in susceptibility to frank disease upon infection is the explanation. In scarlet fever and diphtheria where the exceptions occur, toxin production is a part of the disease picture. The question is raised whether or not a seasonal variation in toxin production is involved. If such were the case, it would be expected that the amplitude of seasonal fluctuation would be the greater one determined by seasonal variation in the potential reservoir of infection, rather than the lesser one which can be best accounted for by seasonal variation in susceptibility to a "constant" reservoir of infection.

Of the group of virus diseases considered in this study, poliomyelitis is the only one in which there is a diminution in the frequency of frank disease in those exposed to the causative agent as warmer climates are approached (as is true of both diphtheria and scarlet fever). In cooler climates, there is a greater amplitude in seasonal variation in the host which, it is inferred, affects not only seasonal variation in susceptibility to frank disease, but also seasonal variation in the potential reservoir of infection (resulting from seasonal variation in multiplication of virus). The question is raised whether or not the exception to the general rule in virus diseases, in the case of poliomyelitis in warmer climates, may not be due in some way to the fact that poliomyelitis has the seemingly paradoxical characteristic of being a disease of the warmer seasons, but of cooler climates.

The amplitude of seasonal variation in scarlet fever, north and south, and of diphtheria and poliomyelitis, south, is equal to the seasonal fluctuation in the bacterial diseases as a group combined with a second amplitude of the same order. It seems, then, that the seasonal fluctuation of scarlet fever and diphtheria may be determined by variations of the same

order in the virus reservoir and susceptibility. In the case of scarlet fever, this is substantiated in part by the observation that the Group A streptococcus carrier rate, unlike the meningococcus carrier rate, has a seasonal fluctuation of the same order of amplitude as that of the bacterial upper respiratory disease group,³ and the now generally accepted fact that production of erythrogenic toxin by the streptococcus varies at different times in different places. It is perhaps more than coincidence that diphtheria, the other exception to the rule for the bacterial upper respiratory disease group, also is a disease in which the production of soluble toxin plays a rôle. It might be postulated that the difference in amplitude between northern and southern diphtheria and northern and southern poliomyelitis is the result of a more pronounced effect of seasonal change on the virus reservoir in cooler climates. This, together with the lesser range of fluctuation in physiologic function in warmer climates, might affect the differences between northern and southern amplitudes.

Summary. The amplitudes of seasonal fluctuation in a number of infectious diseases all fall into 1 of 3 types of curves. The first of these is a curve of low amplitude in which the progression is arithmetic in type. This suggests that in this group of diseases, amplitude of seasonal fluctuation is determined by some simple numerical variable. The close correspondence between this curve and those of a number of seasonal variations in physiologic functions, as well as the close correspondence with the curve representing seasonal variation in attack rate in carriers in meningitis, suggests that the amplitude of seasonal variation in upper respiratory contact bacterial infections may be determined in the main by seasonal variation in susceptibility to infection under a rate of exposure which does not necessarily follow a corresponding seasonal variation.

The second type of seasonal variation in which the progression is roughly geometric suggests the operation of a factor such as

seasonal variation in virus reservoir. This type of curve is seen in certain exceptions to the rule in upper respiratory bacterial and virus diseases, and is of the same order of amplitude as that exhibited by diseases transmitted through intermediary reservoirs, in some of which seasonal variation is believed to be determined in the main by variation in the virus reservoir.

The third type of seasonal curve is one of high amplitude and is equal to the combined amplitudes of the other 2 types of curves. This type of curve is characteristic of virus diseases transmitted directly from human to human, and the inference is made that the amplitude of seasonal fluctuation in these virus diseases is determined by a seasonal variation in susceptibility to infection, which accounts for the smaller part of the seasonal variation in disease (arithmetic) and combined with it seasonal variation of the same period and phase in multiplication of virus, which, in turn, affects transmission in geometric fashion. That susceptibility to infection and "susceptibility to harborage, multiplication and transmission" may be associated is manifest in the epidemiologic behavior of such virus diseases as measles and smallpox.

Perhaps the 3 amplitudes seen in different groups of diseases in exact multiples, and the idea that they are the result of a single influence (season) affecting simul-

taneously one, two or three factors involved, can be most simply illustrated by reversing the phenomenon and the line of reasoning to an epidemiologic chimera where the curves represent an imaginary "disease" occurring in 3 main groups of critters in proportion to the number of legs of the individuals in each group, and in certain exceptions according to the number of feet on the ground. The analogy with still other amplitudes can be extended on the one side to those that do not put their feet on the ground, and do not have the disease; and on the other side to those with many legs and much of the disease; all the way from the whale, with no feet and no disease at all, to the snail, all foot and all disease. (Chart 5.)

Conclusion. Three distinct patterns of amplitude of seasonal variation are found in a number of infectious diseases. In upper respiratory bacterial infections as a group, the amplitudes suggest the operation of a single arithmetic variable consistent with seasonal variation in susceptibility. In a second group, comprising diseases transmitted by intermediary means, the amplitudes are consistent with seasonal variation in the virus reservoir. In a third group, comprising upper respiratory virus infections, the amplitudes lead to the inference that both seasonal fluctuation in susceptibility in the human virus reservoir are determinants.

REFERENCES

1. AYCOCK, W. L., and EATON, P.: The Biseasonal Prevalence of Infantile Paralysis (Acute Anterior Poliomyelitis), *Am. J. Hyg.*, 4, 356, 1924.
2. AYCOCK, W. L., LUTMAN, G. E., and FOLEY, G. E.: Seasonal Prevalence as an Epidemiologic Principle, *Am. J. Med. Sci.*, 209, 395, 1945.
3. AYCOCK, W. L.: Unpublished data, this laboratory.
4. FENGER, F., ANDREW, R. H., and VOLLERTSON, J. J.: Geographic Location and the Iodine Content of the Thyroid Gland, *J. Am. Chem. Soc.*, 53, 237, 1931. Aycock, W. L.: A Study of the Significance of Geographic and Seasonal Variations in the Incidence of Poliomyelitis, *J. Prev. Med.*, 3, 245, 1929.
5. HOSKINS, J. K., RUCHOFF, C. C., and WILLIAMS, L. G.: A Study of the Pollution and Natural Purification of the Illinois River, Surveys and Laboratory Studies, U. S. Pub. Health Service, Bull., No. 171, p. 199, 1927.
6. LUTMAN, G. E.: The Epidemiologic Significance of the Seasonal Prevalence of Disease. Thesis submitted to the Faculty of the Harvard School of Public Health in partial fulfillment of the requirements for the degree of Doctor of Public Health, 1945.
7. MUELLER, J. H., and AYCOCK, W. L.: To be published.
8. U. S. Pub. Health Rep., 1925-1939.

PENICILLIN TREATMENT OF ACUTE SYPHILITIC NEPHROSIS AND IRITIS

REPORT OF A CASE*

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AMONG the visceral manifestations of early syphilis the acute nephrotic syndrome is well recognized.¹⁻³ Although the older methods of treatment usually produced satisfactory results when properly employed, no reports have appeared dealing with the effect of penicillin on this aspect of syphilitic infection. This brief paper reports an instance of secondary syphilis complicated by acute nephrosis and iritis in which penicillin was the sole antisypilitic agent employed.

Case Report. A 29 year old Negress (J. H. H. 307289) was first seen in the Wilmer Eye Clinic on Nov. 15, 1943, because of dimness of vision due to an inflamed, painful right eye of 2 weeks' duration. Pupillary reactions were normal in both eyes and the media were clear. Uncorrected visual acuity was diminished on the right (20/40-1), 20/20 on the left. A diagnosis of conjunctivitis was made, irrigations were prescribed, and she was told to return in 3 days. She was seen again 1 week later in the clinic; in the interim it was found that her blood serologic test for syphilis was positive. Questioning revealed that a blood test done in March, 1942, had been negative for syphilis but that she had since been promiscuous in her relations. Four months before, a small pimple had appeared on her genitalia but this had spontaneously subsided in a few days. No skin rash, alopecia, adenopathy, or dysuria had been observed, but a severe sore throat, present 4 weeks previously, had responded to symptomatic treatment.

Examination disclosed that on the right side the eyelids were edematous; photophobia and lacrimation were extreme. Severe palpebral and bulbar conjunctival injection was seen and the deep scleral vessels were

dilated. Although the cornea was described as clear by the eye consultant and no synechias were noted, the pupil was large and fixed to light (Fig. 1, A). An aqueous ray was present due to numerous circulating points in the anterior chamber (slit lamp examination). The left eye was normal in appearance and pupillary reactions were prompt. Uncorrected visual acuity was further diminished in the right eye (20/50 + 1) but still 20/20 on the left. The oropharyngeal mucous membrane was hyperemic but no mucous patches were seen. Submandibular adenopathy on the right and slight generalized lymph node enlargement were reported. There was a minimal degree of pitting pretibial edema bilaterally. Faint red, slightly pigmented macules were seen on both soles but no other cutaneous lesions characteristic of secondary syphilis were found. The neurologic examination was negative.

Laboratory studies disclosed anemia (13.3 gm. of hemoglobin per 100 cc. of blood) but an otherwise normal hemogram. Blood serologic tests for syphilis were positive, the Eagle flocculation titer being 32 units. Cerebrospinal fluid contained 40 leukocytes per c.mm. and 25 mg. of protein per 100 cc. of fluid. The Wassermann reaction was positive with as little as 0.6 cc. and the colloidal mastic curve was 4311000000. The specific gravity of a voided urine specimen was 1.018. Four-plus albumin was present but a qualitative copper-reduction test was negative. A few erythrocytes and 4 to 6 leukocytes per high power field were seen. On the basis of these findings the patient was admitted to the hospital for the experimental penicillin therapy of secondary syphilis complicated by acute diffuse iritis and the nephrotic syndrome.

The patient was in the hospital 4 days

* The work in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and The Johns Hopkins University.

before specific therapy was instituted; during this observation period the edema of the lower extremities completely subsided. She weighed 72.1 kg. (159 pounds) on admission to the ward. The blood pressure was 118 mm. of mercury systolic and 80 mm. of mercury diastolic. A culture of catheterized urine was sterile. A test of urea clearance done at this time was reported as 110% of normal standard and 97% of normal maximum clearance. Phenolsulfonphthalein excretion was good, 15% of the dye being recovered in 15 minutes and a total of 90% in 2 hours. Twenty-eight mg. of non-protein nitrogen and 242 of cholesterol were present per

lin, 10,000 Oxford units, in aqueous solution, were injected intramuscularly every 3 hours day and night for 60 doses, a total of 600,000 units in 7.5 days. This dosage schedule was selected on an entirely experimental basis. There was no Herxheimer reaction. After the 1st day of treatment the conjunctival injection was appreciably less and ocular pain had significantly decreased. By Dec. 2, lid edema had almost disappeared and blepharospasm had diminished (Fig. 1, *B*). Re-examination with the slit lamp 4 days later showed only a questionable aqueous ray but uncorrected visual acuity remained 20/50 in the right eye; haziness of vision was

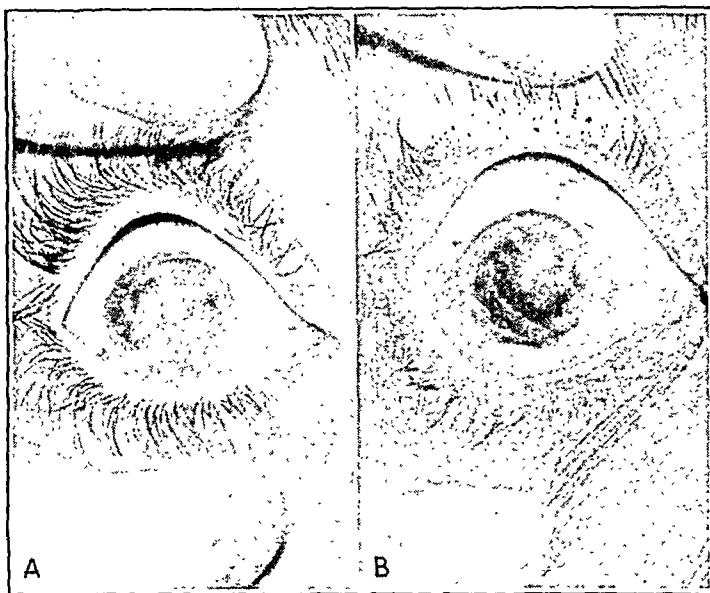


FIG. 1. *A*.—Right eye prior to treatment showing diffuse opacity within the anterior chamber. *B*. On the 4th day of penicillin therapy resolution of opacity is apparent. No residuals were found 708 days after the start of treatment.

100 cc. of blood. Blood chlorides, urea nitrogen, calcium and phosphorus levels were normal. Total serum protein was 6.88 gm. per 100 cc. of blood and the albumin-globulin ratio was 0.87 (Fig. 2). During her first 5 days in the hospital the daily excretion of albumin in the urine rose rapidly from 5 gm. (2.3 gm. per liter) on the day of admission to 20 gm. (7.4 gm. per liter of urine). Hyaline and granular casts were observed in small numbers during this pretreatment period but no erythrocytes were seen. The specific gravity of the urine was 1.025 on admission, a level not exceeded at any time.

Penicillin therapy was begun on the 5th hospital day (Nov. 29, 1943). Sodium penicil-

lin, 10,000 Oxford units, in aqueous solution, were injected intramuscularly every 3 hours day and night for 60 doses, a total of 600,000 units in 7.5 days. This dosage schedule was selected on an entirely experimental basis.

There was no Herxheimer reaction. After the 1st day of treatment the conjunctival injection was appreciably less and ocular pain had significantly decreased. By Dec. 2, lid edema had almost disappeared and blepharospasm had diminished (Fig. 1, *B*). Re-examination with the slit lamp 4 days later showed only a questionable aqueous ray but uncorrected visual acuity remained 20/50 in the right eye; haziness of vision was still a complaint. By Dec. 10, the right eye was said to be completely well; no ocular congestion or subjective symptoms remained. These clinical findings paralleled in a remarkable manner the course of the syphilitic nephrosis, well illustrated by the diminution in the amount of albumin lost daily in the urine as shown in Figure 2. The total fluid and sodium chloride intake was not curtailed at any time. After the 2d day of penicillin treatment casts were not seen in any specimen of urine. On the 4th and 6th days of treatment counts of 2 and 4 erythrocytes per high power field were reported but hematuria was not subsequently noted. The specific gravity of daily urine specimens

varied from 1.019 on the day treatment was started to 1.009 with an average of 1.013. No significant diuresis occurred, the maximum daily urinary output (3725 cc.) being on the 11th day after the initiation of treatment; intake and output were comparable throughout. Body weight fell to 70.3 kg. (155 pounds) on the 2d day of therapy but at the time of discharge she weighed 73 kg. (161 pounds).

clearance was 95 and 86 % of normal standard clearance (normal tests). Spinal fluid taken at the end of the hospital stay contained only 4 leukocytes per cmm. of fluid and the protein content was unchanged. The Wassermann reaction was now negative in all dilutions, however, as was the colloidal mastic curve. The blood serologic titer underwent a series of interesting changes. The titer was 32 Eagle units

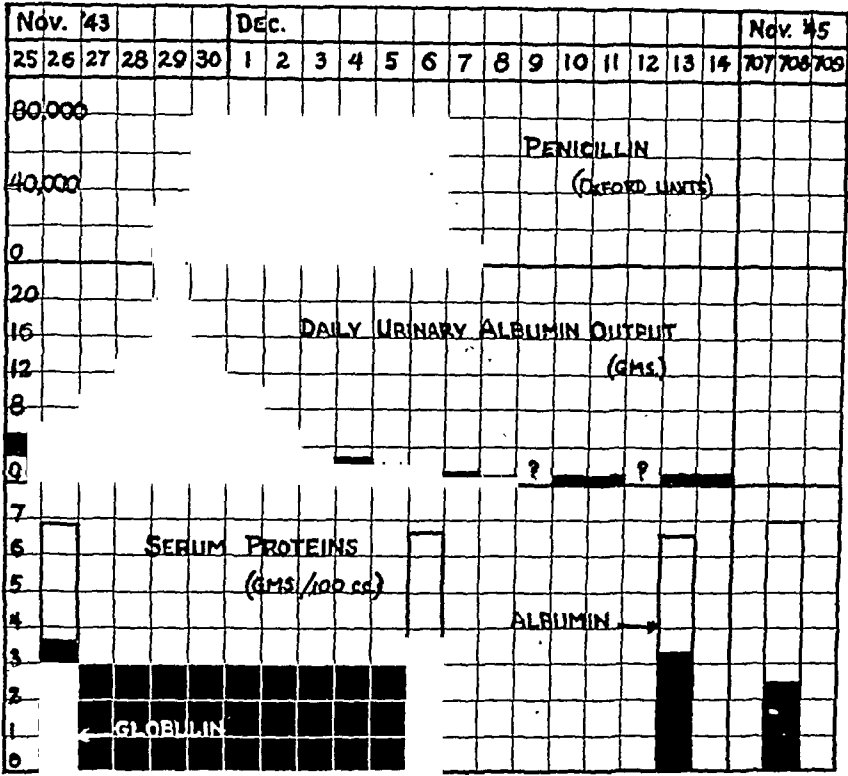


FIG. 2.—Effect of penicillin on blood and urine findings in acute syphilitic nephrosis.

Daily blood pressure determinations were, without exception, lower than the admission one; the average systolic pressure during her hospital stay was 102.3 mm. of mercury, whereas the mean diastolic pressure was 68.9 mm. of mercury. The hemoglobin content of the blood was essentially unchanged during her stay on the ward and non-protein nitrogen levels at no time exceeded 32 mg. per 100 cc. of blood. Prior to discharge the total serum proteins had fallen to 6.56 gm. per 100 cc. of blood, but the albumin-globulin ratio was greater than unity (1.06). Phenol-sulfonphthalein excretion was reported as 40% in 15 minutes with a total of 80% of the dye being recovered in 2 hours; urea

prior to treatment; it rose to 128 units on the 6th and to 256 units on the 14th day after the start of therapy. The next examination, done 114 days after penicillin was begun, yielded an Eagle titer of 4 units; at 142 days a positive reaction was obtained with whole serum only (titer of 1). By 163 days the blood serologic test was negative and remained so in each of 8 subsequent tests performed at various intervals, the last one being on June 20, 1945, 570 days after the start of treatment. On Nov. 5, 1945, 708 days after her first penicillin, this patient was readmitted to the ward for evaluation. She appeared to be in excellent general health and her body

weight was 77 kg. (169.4 pounds). Blood pressure was 116 mm. of mercury systolic and 90 mm. diastolic. According to an eye consultant (Dr. Joseph S. Haas) the anterior chambers were of average depth and were optically inactive. The pupils were round, equal, and responded readily to light and accommodation. The iris stroma was similar in each eye. Uncorrected visual acuity was 20/20 bilaterally. The final impression was "complete healing of right iritis with no residuals."

From the laboratory standpoint the improvement had been equally well sustained. Two blood serologic tests for syphilis were negative. The spinal fluid contained 2 leukocytes per cmm. and 17 mg. of protein per 100 cc. of fluid. The Wassermann reaction was negative in all dilutions as was the colloidal mastic test. Microscopic examination of the blood disclosed a normal hemogram except for hypochromic anemia: 4,830,000 erythrocytes per cmm. of blood but only 11.8 gm. of hemoglobin per 100 cc. The serum proteins totalled 7 gm. per 100 cc. of blood and the albumin-globulin ratio was 1.60 (see Fig. 2). Determinations of non-protein nitrogen, total cholesterol, and blood urea nitrogen were normal.

An urinalysis on the day of admission to the ward contained a faint trace of albumin but was otherwise normal; three subsequent analyses were entirely negative. A culture of urine was reported as containing *Microaerophilus alpha streptococcus* which was regarded as a contaminant. Tests of kidney function were entirely satisfactory. Ability to dilute and concentrate urine was demonstrated by samples with specific gravities of 1.002 and 1.023 respectively. Urea clearance was 130% of normal standard clearance. Results of the phenolsulfonphthalein test were excellent; 40% of the dye was excreted in 15 minutes, a total of 95% in 2 hours.

Discussion. The diagnosis of nephrosis depends clinically on the presence of albuminuria, transient edema, changes in the serum proteins, especially the albumin fraction, and either absent or non-persistent hypertension or nitrogen retention. Casts in the urinary sediment are seldom numerous and erythrocytes are rare. Such tests of kidney function as urea clearance and phenolsulfonphthalein excretion are

characteristically normal.⁵ The most common occurrence suggestive of renal damage in syphilitic patients is a simple, slight albuminuria unaccompanied by other evidences of nephropathy. Some degree of albuminuria was found, for example, in 7.1% of 1040 patients with syphilis studied with regard to kidney involvement. No patients with primary lesions but 5 of 61 (8.2%) with secondary manifestations had albumin in the urine.² A small percentage of these progresses to the clinical picture previously described, indistinguishable from idiopathic nephrosis except that appropriate antisiphilitic treatment causes a diminution or disappearance of the albuminuria.¹

Prior to the advent of penicillin each of the accepted antisiphilitic drugs had been used singly and in various combinations with success. Herrmann and Marr² remark, however, that "each drug has been noted in some case or another to have increased the albuminuria or other signs of renal involvement, and especially has this been so when the drug was administered in its usual doses. It must be remembered that in all antisiphilitic therapy the damaged renal tissue of syphilitic nephropathies is more vulnerable than normal kidney parenchyma." This has been further emphasized by Moore⁴ who points out that large initial doses of the older drugs were known to provoke severe Herxheimer reactions which "may result with anuria, increasing edema and nitrogen retention, and even uremia." For these reasons, as in other types of visceral syphilitic disease,⁶ the essentially non-toxic properties of penicillin recommend it highly. Although Herxheimer reactions are frequent in patients with early syphilis treated with this antibiotic substance, they are characteristically mild and it is felt that they may be safely disregarded because no additional chemical insult is imposed upon the injured kidney parenchyma.

The eye lesion in this patient is also of considerable interest for two reasons. Iritis has been the most important of the

ocular complications of early acquired syphilis, occurring in about 4% of all cases of secondary syphilis.⁷ In this patient, the response to penicillin therapy was dramatic, the involved eye being objectively and subjectively well within 11 days after the start of treatment. Woods⁷ has emphasized the tendency to ocular relapse in these patients following inadequate therapy by the older methods. Fortunately, with this antibiotic agent the entire treatment may be given during a short period of hospitalization; even irresponsible patients have a minimal opportunity to lapse. Although no evidence of ocular relapse was present in the patient here reported after a follow-up period of 708 days, the problem of the frequency of such occurrences in patients with penicillin-treated syphilitic iritis is one requiring statistical attack.

The efficacy of penicillin in acute syphilitic nephrosis and iritis is well illustrated in the case presented here. In the light of subsequent experience the experimental

total dosage originally chosen of only 600,000 Oxford units would be considered inadvisable; several times that amount would now be employed. It is significant, however, that not only did that relatively small dosage produce rapid and sustained improvement in the complications but it apparently cured the underlying syphilitic infection itself, as evidenced by clinical and serologic negativity almost 2 years after therapy.

Summary. A patient with secondary syphilis complicated by acute nephrosis and iritis is reported. Treatment was experimental and consisted of the intramuscular administration of 600,000 Oxford units of sodium penicillin in 7.5 days. Dramatic immediate and sustained improvement of both complications ensued. The underlying syphilitic infection itself was apparently cured, as judged by clinical and serologic negativity 708 days after the initiation of treatment. The advantages of penicillin over the older methods of therapy are discussed.

REFERENCES

1. BAKER, B. M.: The Relation of Syphilis to Nephritis, *Bull. Johns Hopkins Hosp.*, **65**, 196, 1939.
2. HERRMANN, G., and MARR, W. L.: Clinical Syphilitic Nephropathies: a study of new cases and a survey of reported cases, *Am. J. Syph. and Neurol.*, **19**, 1, 1935.
3. MOORE, J. E.: *The Modern Treatment of Syphilis*, 2d ed., Springfield, Ill., Charles C Thomas, p. 243, 1943.
4. MOORE, J. E.: Reference 3, p. 242.
5. SMETANA, H. F.: A Discussion on Nephrosis and Nephritis, *Urol. and Cutan. Rev.*, **48**, 580, 1944.
6. TUCKER, H. A., and DEXTER, D. D.: Penicillin Treatment of Gummatous Hepatic Syphilis (to be published).
7. WOODS, A. C.: Syphilis of the Eye, *Am. J. Syph., Gonorr. and Ven. Dis.*, **27**, 133, 1943.

SALMONELLA SUIPESTIFER INFECTION IN CHILDREN

A REPORT OF EIGHTEEN CASES

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QUITE a number of isolated cases of *Salmonella suipestifer* infection among infants and children have been reported,^{8,11,14,15,16,19,24,26,28,31} as well as outbreaks of food poisoning due to the *Salmonella* group, but relatively few articles have dealt with any appreciable number of cases.

In Harvey's¹⁷ series of 21 cases there were 14 children, while Goulder *et al.*¹⁴ reported 6 cases in children. Gajzago and Gottché's¹² report included 6 cases of this type of infections (with osteomyelitis in all 6), while Kuttner and Zepp²⁴ reported 7 such cases. During the past 8 years, 18 cases of *S. suipestifer* infections were admitted to this hospital. The average annual admission rate during this period was 2084 cases. It appears thus, that this disease is relatively rare in the Philadelphia area. The purpose of this paper is to report these 18 patients in some detail. Table 1 lists the important features of these cases.

History of the Illness. On the basis of the information obtained from the case histories, all of the cases seemed to be sporadic infections. None were of the so-called "food poisoning" type (more correctly termed *Salmonella* infections), where a common source of infection like contaminated food, could be found.^{18,32,34} No other cases occurred in the same households as far as could be determined, nor were similar infections subsequent to the patient's return home from the hospital later reported in possible contacts.

Age. The range of age was between 4 months and 10 years. Only 2 of the children were over 2 years of age, while

1 child was 2 years old, and the remainder were under 2 years of age.

Signs and Symptoms. Gastro-intestinal symptoms: only 4 of the patients gave a history of vomiting, or vomited while ill in the hospital. There were only 9 patients who had diarrhea, 6 of a mild character, while 1 had diarrhea for 25 days. One had gross blood in the stools.

Fever. The average number of days of fever, with the exception of the patient who died, was 3½ days. One patient had fever for 24 days, but was not very ill.

Infection of the Respiratory Tract. There were 12 patients who had a nasopharyngitis on admission. Nine of the 18 cases had either unilateral or bilateral otitis media (suppurative) on admission, or before they recovered. Five cases showed pulmonary signs by physical examination, and 2 of these had bronchopneumonia as shown by Roentgen ray examination.

Course. There were 2 deaths among the group. One of these was found at postmortem examination to have bilateral polycystic kidneys. The other patient who died was a premature infant who had diarrhea 1 week prior to admission. The patient with petechiæ was acutely ill, while those patients with otitis media and infection of the respiratory tract were moderately sick. However, most of the patients were not very ill, and the disease in these ran a short, benign course. Of the 14 patients with positive blood cultures only 7 had diarrhea. Enlargement of the spleen was noted in only 3 patients, and none of the patients developed "rose spots."

Treatment. The therapeutic aspects of suipestifer infection, in common with those of most other infections produced by gram-negative bacilli, leave a great deal to be desired. Concerning the *Salmonella* organism there are available certain laboratory studies which would seem to point the way to the proper clinical approach. However, the limited number of clinical reports dealing with specific therapy do not permit a hopeful outlook concerning correlation between the results obtained in the test tube and in the patient.

Interesting studies, very largely of a laboratory nature, have been made relative to serums, vaccines, and bacteriophage in a variety of *Salmonella* infections.^{2,23} Specific antisera against certain *Salmonella* organisms have been produced which will protect animals against infection or will prevent death in animals after the administration of otherwise lethal doses of organisms. Specific antisera are not generally available for use against suipestifer infection in the human. Vaccines in some instances yield high antibody titers and good evidence of protection, but because of the low incidence of the disease they find little application in clinical practice where treatment and not immunization is the usual problem. Mice can be protected against many types of *Salmonella* organisms by the use of specific bacteriophage, but results in humans are inconclusive and time is always required for the preparation of a specific phage.

Whenever suipestifer infection localizes, with abscess production, surgical drainage is indicated and is usually followed by satisfactory results.^{8,33,37}

In vitro experiments indicate that both sulfadiazine and sulfathiazole are effective inhibitors of suipestifer, and that they are even bactericidal under certain specific conditions.^{27,35} *In vitro*, suipestifer is the most susceptible of all the common *Salmonella* organisms.^{27,35} In certain synthetic media either sulfathiazole or sulfadiazine in a concentration of 1 mg. per 100 cc. of media is lethal for suipestifer in

24 hours. However, in broth culture, to produce the same lethal effect, 10 to 50 times as much was required depending upon the broth used. This is but another example of the influence of substrate on chemotherapeutic effectiveness.³⁵

If sulfathiazole or sulfadiazine is to be used in human suipestifer infections it would seem rational to utilize a drug capable of giving adequate blood levels and at the same time capable of maintaining a high concentration in the lumen of the bowel. This is based upon the fact that most cases are both septicemic and at the same or at some other time, enteric. Until recently it was believed that the combination of sulfathiazole and succinyl-sulfathiazole would most satisfactorily meet the above requirements. It is possible, however, that sulfathiazole alone is as effective as the combination.

In the present series of 18 cases, 12 received sulfonamide therapy and 6 had none. Of the 12 treated with sulfonamides, 8 received sulfathiazole only, 1 received succinyl-sulfathiazole only, and 1 received sulfadiazine, sulfathiazole, and succinyl-sulfathiazole. In addition, 1 patient received sulfathiazole and sulfaguandine and 1 other received sulfathiazole and sulfapyridine. In comparing these 2 very small groups of patients no clinical effect upon the infection could be ascribed directly to the compound used. In terms of fever, symptoms, and cultures of the blood and stools, there was no significant difference between those treated and those not treated with sulfonamides. All cases received such supportive therapy of a non-specific nature as was required. The restoration and maintenance of electrolyte and fluid balance plus blood transfusion when it seemed indicated, were the basis for this supportive treatment. The group is obviously too small to permit judgment concerning the value of sulfonamide therapy. It is felt however that the use of sulfathiazole or sulfadiazine represents a rational chemotherapeutic approach to the treatment of suipestifer infection.

It is hardly possible to conclude any consideration of therapy of a bacterial disease without mentioning the effect of antibiotic substances. In general the available antibiotic substances are not effective against *Salmonella* organisms. The reasons for this lack of effectiveness are now rather well understood.^{9,10,13,35} Penicillin is not effective against *suipestifer* not, indeed, against most pathogenic gram-negative species. Streptomycin has been shown to be effective in protecting mice against *Salmonella schottmüller*.²² Within proper dose ranges this protection is complete against otherwise uniformly lethal doses of the organism. The value of streptomycin in *suipestifer* infections remains to be determined.

Comment. The mildness and relative infrequency of gastro-intestinal symptoms is worthy of note. Only 9 patients had diarrhea, and this was of a mild character, except in the premature infant who died. The latter patient was the only one who had gross blood in the stools. In a report of 7 cases by Kuttner and Zepp,²⁵ 1 had a nasopharyngitis, 1 had otitis media, 1 had acute tonsillitis and bronchopneumonia. None had diarrhea. In another report by Kuttner and Zepp²⁴ of 4 cases of *S. suipestifer*, 1 was admitted to the hospital with bronchopneumonia, and another had a nasopharyngitis; while the other 2 had pyarthrosis, but none of the cases had diarrhea.

Invasion of the ears and respiratory tract in *S. suipestifer* infections has been noted with varying frequency by various authors. Hormaeche *et al.*,²⁰ who made a comprehensive study of diarrhea due to the *Salmonella* group of organisms among infants and children, obtained 10.1% positive pharyngeal cultures in 152 cases. Included in these cases were 67 children with draining ears, and of these, there were 20.89% who had positive cultures from the aural discharge. These factors could be important as regards the spread of *Salmonella* infections in a hospital ward. Gouley and Israel¹⁵ cited the literature on 14 sporadic cases.

Of these there were 7 cases who had pneumonia. Bullowa⁷ was able to isolate the causative organism from the sputum of a case of pneumonia due to *S. suipestifer*. Bosch⁶ has stressed the increased incidence of *S. suipestifer* infections in the presence of pneumonia and malaria.

In spite of the high incidence of bacteremia among our patients (Table 1), no case developed evidence of localization of the infection such as osteomyelitis or arthritis. This was surprising in view of the many types of complications in *S. suipestifer* infections that have been reported.^{8,11,12,14,15,16,19,21,24,26,28,29,30,31} In the other reports, bone and joint involvement seemed to be frequent. Harvey¹⁷ stated that from his study of reported cases of *S. suipestifer* infections, bone and joint involvement occurred in about 20% of the total. All 6 of the cases reported by Gajzago and Gottché¹² had osteomyelitis. These authors collected the data from 34 cases of *S. suipestifer* in children that had been reported from various countries since 1920, and found that 12 of the 34 had osteomyelitis. The number of cases in these reports showing positive blood cultures seems fairly high, in light of the mildness of the clinical picture in most of the patients. Of the 71 cases collected by Harvey,¹⁷ 44% had positive blood cultures, and 5 of the 6 children in Goulder's¹⁴ series were positive. Bacteremia was present in only 10.34% of Hormaeche's²⁰ cases.

The bacteria are not difficult to grow from cases of bacteremia, but proper identification of the specific organism in *Salmonella* infections may, at times, be a difficult procedure. This is largely due to the presence of separate antigens in the body, in contrast to the flagella of the organism, and because the agglutination behavior for the 2 antigens is entirely different. Also, many of the organisms may exist in 2 phases, a specific phase, with flagellar antigens peculiar to itself, and a group phase, in which the flagellar antigens are common to many members of the *Salmonella* group of bacteria. *S.*

TABLE 1.—EIGHTEEN CASES OF SALMONELLA SUIPESTIFER INFECTION (SALMONELLA CHOLERÆSUIS) (HOG CHOLERA)

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Age Y: Years		1	2	10	10	18	5	1	1½	4	1½	1	1½	17	10	9	6	1
M: Months																		
Sex	M	M	F	M	M	F	M	M	F	M	F	F	F	M	Y	M	M	M
Duration of fever (total)	6	11	5	24	3	7	3	18	15	8	4	15	4	-	2	1	2	16
Upper respiratory infection	+	+	+	+	-	+	+	+	+	+	+	+	+	-	-	+	-	-
Otitis media	+	-	+	+	-	+	-	+	+	+	-	+	-	+	-	-	-	-
P.E. lungs	R	R	R	Pn	-	-	-	-	Fn	R	R	+	-	-	-	-	-	-
Splenomegaly	+	+	-	+	-	-	-	-	+	-	-	+	+	-	-	-	-	-
Vomiting	+	+	-	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-
Diarrhea	+	-	-	+	-	-	-	+	-	+	+	-	+	-	-	-	+	+
Blood in stool	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-
Blood culture	+	+	+	+	-	+	+	+	+	+	+	+	+	ND	-	+	-	+
Stool culture	-	+	-	+	+	+	-	-	-	+	+	-	-	+	+	ND	+	ND
Blood agglutination	ND	ND	+	+	ND	+	-	-	+	+	+	ND	+	ND	ND	-	+	-
Recovered or died	Rec.	Rec.	D	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	D

R, rales; Pn, pneumonia (by Roentgen ray); ND, not done; Rec., recovered; D, died (bilateral polycystic kidneys at autopsy).

suipestifer, American type, can exist in both the group and specific phase, while *S. suipestifer*, European type, can exist in the group phase.

Goulder *et al.*¹⁴ performed agglutination tests on the sera of normal individuals to determine if they had agglutinins for *S. suipestifer* and obtained negative results. However, high agglutination titers were found in most of the *S. suipestifer* cases, and this titer persisted for a period of time ranging from a few months to 6 years after the infection. Harvey¹⁷ was able to find reported titers as high as 1 to 12,800, and in his series 88% of the patients had a titer higher than 1 to 320

examination, and 3 others with pulmonary signs by physical examination.

None of the patients developed an infection in bones or joints. Of blood cultures, taken on all but 1 patient, 14 were positive in 17 cases. Stool cultures were done on all but 1 patient and 7 were reported as positive. Blood agglutination studies were made too infrequently to be of value.

There were only 2 deaths in the group. One of these had bilateral polycystic kidneys, while the other was a premature infant who had diarrhea at home for 1 week before admission.

Treatment of *suipestifer* infections in-

TABLE 2.—FERMENTATION REACTION OF BACTERIUM PARATYPHOSUS B AND SALMONEILLA SUIPESTIFER

	<i>B. paratyphosus B</i>	<i>S. suipestifer</i>	
		American	European
Production of gas	+	+	+
Mannitol	+	+	+
Dulcitol	++++	++++	++++
Sorbitol	+	+	+
Inositol	++++	0	0
Maltose	+	+	+
Arabinose	+	0	0
Rhamnose	+	+	+
Xylose	++++	+	+
Trehalose	+	0	0
Dextrin	+	+	+
Litmus milk	Alk	Alk	Alk
Production of H.S.	+	0	—
Bitter rhamnose	++++	0	0
Stern glycerol	++++	0	0
d-tartrate	++++	+	+
Utilize citrate agar	+	0	0
Utilize tartrate agar	0	+	+

+, positive; 0, negative; + + + +, variable or delayed fermentation.

* Bornstein, S.: The State of the Salmonella Problem, *J. Immunol.*, 46, 439, 1943.

by the 4th week. In 1 of these, a titer of 1 to 250 was still present 2 years after the illness.

Some of the fermentation characteristics of *S. suipestifer* and *B. paratyphosus* are shown in Table 2.

Summary. Clinical and bacteriologic data on 18 sporadic cases of *S. suipestifer* infection are presented.

Vomiting occurred in only 4 patients, while there were 9 who had diarrhea. One of the patients had gross blood in the stools.

There were 12 patients who had an infection in the respiratory tract. Of these, there were 9 with otitis media, 2 with bronchopneumonia by Roentgen ray

clude proper parenteral administration of necessary fluids and electrolytes in the more severe cases accompanied by diarrhea. The administration of sulfathiazole or sulfadiazine is indicated on the basis of experimental laboratory data, but in the series of cases here presented, it was not possible to demonstrate any well-defined effects which could be directly ascribed to the administration of sulfonamides. In general, the available antibiotic substances are not effective against *Salmonella* organisms. The effectiveness of streptomycin is currently under investigation in *Salmonella* infections. This substance seems more promising than compounds previously tested.

REFERENCES

1. BEAMER, P. R.: *Proc. Soc. Exp. Biol. and Med.*, **49**, 418, 1942.
2. BOIVIN, A., and RICHOU: *Compt. rend. Soc. de biol.*, **131**, 1130, 1939.
3. BORNSTEIN, S., and SCHWARZ, H.: *AM. J. MED. SCI.*, **204**, 546, 1942.
4. BORNSTEIN, S.: *J. Immunol.*, **46**, 439, 1943.
5. BORNSTEIN, S., and STRAUSS, L.: *Proc. Soc. Exp. Biol. and Med.*, **46**, 112, 1941.
6. BOSCH, W. G.: *Geneek. tijdschr. v. Nederl.-Indie*, **68**, 715, 1928.
7. BULLOWA, J. G. M.: *Med. Clin. North America*, **12**, 691, 1928.
8. CLIFTON, W. M., and WERNER, M.: *Am. J. Dis. Child.*, **55**, 553, 1938.
9. DUBOS, R. J., and LUCH, J. M.: *Ann. Rev., Biochem.*, **11**, 659, 1942.
10. DUBOS, R. M.: *J. Am. Med. Assn.*, **124**, 653, 1944.
11. FORSTER, D. E.: *AM. J. MED. SCI.*, **197**, 234, 1938.
12. GAJZAGO, D., and GOTTCHE, O.: *Am. J. Dis. Child.*, **63**, 15, 1942.
13. GARDENER, A. D.: *Nature*, **146**, 837, 1940.
14. GOULDER, N. E., KINGSLAND, M. F., and JANEWAY, C. A.: *New England J. Med.*, **226**, 127, 1942.
15. GOULEY, B., and ISRAEL, S. L.: *Arch. Int. Med.*, **53**, 699, 1934.
16. GUTHRIE, K. J.: *Arch. Dis. Child.*, **16**, 269, 1941.
17. HARVEY, A. M.: *Arch. Int. Med.*, **59**, 118, 1937.
18. HEIMANN, W.: *Centralbl. f. Bakt. (Abt. 1)*, **66**, 211, 1912.
19. HENDERSON, W. C.: *J. Am. Med. Assn.*, **119**, 259, 1942.
20. HORMAECHE, E., SURRACO, N. L., PELUFFO, C. A., and ALEPO, P. L.: *Am. J. Dis. Child.*, **66**, 539, 1943.
21. JAGER, B. V., and LAMB, M. E.: *New England J. Med.*, **228**, 299, 1933.
22. JONES, D., METZGER, H. J., SCHATZ, A., and WAKSMAN, S.: *Science*, **100**, 1944.
23. KRUEGER, A. P., and SCRIBNER, E. J.: *J. Am. Med. Assn.*, **116**, 2160, 1941.
24. KUTTNER, A. G., and ZEPP, H. D.: *J. Am. Med. Assn.*, **101**, 269, 1933.
25. KUTTNER, A. G., and ZEPP, H. D.: *Bull. Johns Hopkins Hosp.*, **51**, 373, 1932.
26. LANGWILL, A.: *Lancet*, **2**, 1158, 1921.
27. LAWRENCE, C. A.: *Proc. Soc. Exp. Biol. and Med.*, **44**, 162, 1942.
28. LYON, G. M., and FOLSOM, T. G.: *West Virginia Med. J.*, **37**, 249, 1941.
29. NAVORRO, D., WHITE, P. B., DYKE, S. C., and SCOTT, W. M.: *Lancet*, **2**, 868, 1929.
30. NETTER, E. R.: *J. Pediat.*, **23**, 562, 1943.
31. RAVITCH, M. M., and WASHINGTON, J. A.: *J. Am. Med. Assn.*, **109**, 1122, 1937.
32. SCOTT, W. M.: *J. Hyg.*, **25**, 406, 1926.
33. STEVENSON, D. L.: *Lancet*, **2**, 569, 1938.
34. STEWART, H. C., and LITTERE, W.: *J. Am. Med. Assn.*, **89**, 1584, 1927.
35. STRAUSE, E., and FINLAND, M.: *Proc. Soc. Exp. Biol. and Med.*, **47**, 428, 432, 1941.
36. WAKSMAN, S. A.: *Bact. Rev.*, **5**, 231, 1941.
37. WALKER, I. J., WEISS, S., and NYE, R. W.: *New England Med. J.*, **214**, 567, 1936.

THE INCIDENCE OF PALPABLE PULSATIONS IN CONVALESCENT TRENCH FOOT

AN ANALYSIS OF 500 PATIENTS AT AN ARMY GENERAL HOSPITAL

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THE criteria for a diagnosis of trench foot after the acute symptoms have subsided are not clearly defined. The diagnosis often depends solely on a reliable history. In the diagnosis of peripheral vascular diseases in general, palpation for pulsations of the peripheral arteries is an important clinical procedure and may give a great deal of information. An absent pulsation may be seen in spasm or as a result of organic changes in the palpated vessel. It may also indicate a normal anatomic deviation. In the course of studying some of the diagnostic criteria of convalescent trench foot we have been struck by the high incidence of good peripheral pulsations, often in the face of extensive damage and gangrene of the foot.

To investigate this clinical impression, the dorsalis pedis and posterior tibial pulsations of 500 soldiers hospitalized for trench foot at an Army General Hospital were studied. Each soldier was convalescing from either a moderate or an advanced degree of trench foot.* A moderate type was characterized by a typical history of exposure with skin and soft tissue changes but without evidence of gross gangrene. An advanced type was characterized by gangrene with subsequent loss of foot substance. There was an average interval of 6 months from the time of onset of the disease to the date of this study. The study was limited to white soldiers, and the average age was 25. The majority of the patients were from infantry units and prior to the time of hospitalization no soldier had complained of any significant

circulatory disturbance of the lower extremities. The pulsations were graded as "palpable" or "not palpable." Where a pulsation was weak, faint, or a slight distance from the usual location it was considered palpable.

The findings are shown in Table 1. Of the 500 patients examined, 442 (88.4%) had a palpable right dorsalis pedis pulse and 58 (12.6%) an absence of this pulse. The right posterior tibial pulse was palpable in 486 (97.2%) and absent in 14 (2.8%). On the left side similar figures were obtained. The left dorsalis pedis pulse was absent in 72 (14.4%) and the left posterior tibial pulse was absent in 9 (1.8%). There was an absence of both dorsalis pedis pulses in 29 (5.8%) patients and an absence of both posterior tibial pulses in 4 (0.8%). An absence of both posterior tibial and dorsalis pedis pulses on the same side was found in only 3 patients. No patient of this series demonstrated absence of pulsations of both the dorsalis pedis and posterior tibial arteries of both feet.

A clinical study dealing with the presence of pulsations is not without error and is subject to certain criticism. In the first place, the detection of a pulsation depends to a large extent on the efficiency and experience of the examiner. Moreover, the environment in which the examination is performed can influence the results. A cold room, for example, can cause constriction of an artery rendering it barely palpable or impalpable. Age, sex and race are further variables. Emo-

* No attempt was made to differentiate between trench foot and frost-bite. It is generally agreed these 2 conditions are related and a similar mechanism operates in each.⁵

tional influences, such as seen in anxiety states, are important and may influence the caliber of a peripheral vessel. The physical condition of the patient at the time of the examination must also be considered. Such conditions as local deformities, varicosities, edema, and obesity may make it difficult to palpate a normally located vessel. Finally, the arterial supply of the human foot is normally subject to wide anatomic variations.^{6,7}

With these limitations in mind, an attempt was made to correlate the incidence of dorsalis pedis and posterior tibial pulsations in the trench foot patients with a

sent pulsations of the foot in the 2 groups was found.

Comment. Trench foot achieves special prominence in time of war. The clinical observation of extensive tissue damage in soldiers suffering from trench foot in the presence of good pulsations has long been known. Larrey, Napoleon's Surgeon General, in 1812,³ noted that trench foot is not to be confused with ordinary gangrene. To quote: "I have seen examples where a greater or less part of the skin of the foot has been mortified without the vessels having lost their vitality." More recently, Lesser,⁴ in a study of the casualties of the

TABLE 1.—INCIDENCE AND ABSENCE OF PULSATIONS IN 500 PATIENTS WITH CONVALESCENT TRENCH FOOT

	Palpable		Not palpable	
	No.	%	No.	%
Dorsalis pedis (right)	442	88.4	58	11.6
Dorsalis pedis (left)	428	85.6	72	14.4
Posterior tibial (right)	486	97.2	14	2.8
Posterior tibial (left)	491	98.2	9	1.8
Dorsalis pedis (bilateral)	471	94.2	29	5.8
Posterior tibial (bilateral)	496	99.2	4	0.8
Dorsalis pedis and posterior tibial (same side)	497	99.4	3	0.6

TABLE 2.—TABULATION SHOWING ABSENT PULSATIONS OF THE FOOT IN 908 NORMAL CONTROLS AS COMPARED WITH 500 TRENCH FOOT PATIENTS

	Control		Trench foot	
	No.	%	No.	%
Dorsalis pedis (right)	114	12.6	58	11.6
Dorsalis pedis (left)	132	14.5	72	14.4
Posterior tibial (right)	20	2.2	14	2.8
Posterior tibial (left)	18	2.0	9	1.8
Dorsalis pedis (bilateral)	25	8.3	29	5.8
Posterior tibial (bilateral)	9	1.0	4	0.8
Dorsalis pedis and posterior tibial (same side)	5	0.5	3	0.6

similar group of healthy soldiers. The same medical officer (J. J. S.) examined both groups and the same criteria for the presence or absence of a pulse were used. The control group was made up of 908 white soldiers picked for the infantry. The average age was 20. The examination was part of the processing for overseas assignment, and as far as could be ascertained, no soldier in this group had circulatory complaints affecting the lower extremities.

The absence of pulsations in the group of controls is comparatively shown with the trench foot patients (Table 2). The similarity of results is striking. No significant difference in the incidence of ab-

Attu campaign, reported: "In all cases the peripheral arterial pulses were of excellent quality." In Lesser's series there were 25 patients with extensive sepsis and gangrene.

Without going into the details of the pathogenesis of this condition, it is generally agreed that, initially at least, there are profound changes in the peripheral blood-vessels. Cold is a powerful vasoconstrictor both locally and reflexly.⁵ During mild exposure to cold the chilled tissues require little oxygen and no damage is sustained on recovery. On prolonged exposure, however, there is anoxia and injury to the capillary walls resulting in increased permeability, exudation and

edema. With restoration of temperature the arterioles relax and with the increased blood flow there is transudation of plasma and even of blood through the damaged capillaries. It is in this period of circulatory restoration that occlusion of the smaller vessels occurs with formation of red blood cell clots.² The smaller arterioles and veins may demonstrate, on pathologic examination, almost complete obliteration of their lumen. The larger arteries are rarely involved.¹

instituted and he was eventually transferred to the United States. When seen at this General Hospital the first and second toes of the left foot presented a black gangrenous appearance. The right foot was essentially negative to examination. On March 20, under spinal anesthesia, the first and second distal phalanx of the left foot were amputated. Figure 1 demonstrates an occlusion of one of the smaller arterioles seen on microscopic section* of one of the amputated toes. It should be mentioned that in spite of the gangrenous changes the palpable

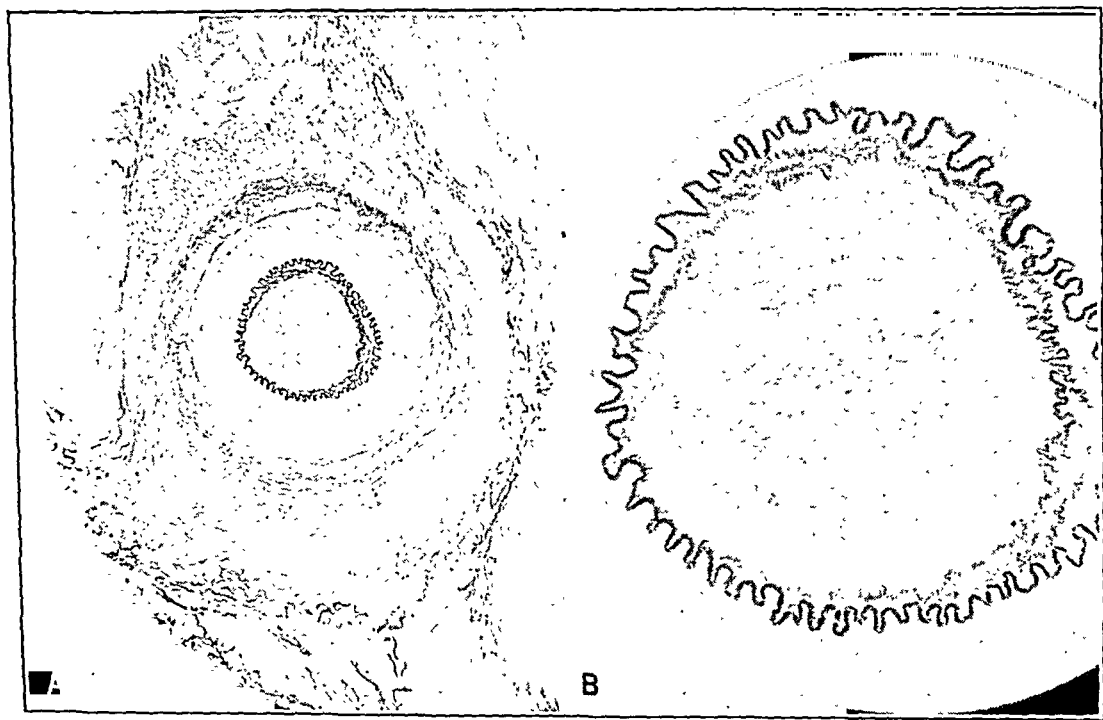


FIG. 1.—A, Photomicrograph of an occluded arteriole showing recanalization. Section taken from an amputated toe of a soldier suffering from severe trench foot. Orcein stain. ($\times 100$.) B, Photomicrograph of same arteriole under higher magnification. ($\times 440$.)

The following case history is illustrative:

Case Report. A 23 year old white Pfc. was admitted to the U. S. A. General Hospital, Camp Butner, N. C., on Mar. 1, 1945, with a diagnosis of trench foot severe, bilateral. Between Jan. 1 and Jan. 4, 1945, he was immobilized in a foxhole while taking part in combat near Bastogne, Belgium. During this period the soldier had no opportunity to change his socks or shoes. On arrival at an Evacuation Hospital both feet were swollen, discolored and lifeless. The standard treatment for trench foot was

pulsations of the foot of this patient were excellent. The dorsalis pedis and posterior tibial arteries were both full and bounding.

The effect of cold was experimentally studied by Talbott⁹ in therapeutic hypothermia. Following exposure to this artificial type of cold one of the first effects observed was an obliteration of the peripheral venous channels so that it eventually became impossible to withdraw venous blood. As the hypothermia was continued constriction of the larger arteries occurred

* Lt. Matthew Block, M.C., A.U.S., performed the microscopic studies.

so that it was difficult to obtain a blood pressure reading. The blood pressure and pulse were unobtainable for several hours, yet there never was any evidence of a thrombus developing in the lumen of the artery as a complication.

Oscillometric studies in this condition reveal no abnormalities, since the oscillometer reflects the pulsation of the larger arteries. Trench foot is essentially a disease of the smaller arterioles and capillaries; and only in extreme cases are the larger arteries involved to the point of occlusion. An occlusion, therefore, of the dorsalis pedis or posterior tibial arteries in a patient who previously demonstrated good pulsations in these arteries would tend to speak against the diagnosis of the usual type of trench foot. It should be remembered that normally the arterial circulation of the foot is subject to wide variations. In a group of healthy soldiers recently studied,⁷ over 13% demonstrated an absence of 1 or more pulses of the foot. However, it was extremely unusual to find an absence of both dorsalis pedis and posterior tibial pulses on the same side. Therefore, whenever this combination is found a serious attempt should be made to rule out other diseases of the peripheral vascular system. Recently 2 patients suffering from Buerger's disease were evacuated to this hospital with a diagnosis of trench foot. These patients, however, demonstrated an absence of both the

dorsalis pedis and posterior tibial pulsations on one side, and it was this observation which eventually led to the correct diagnosis. Trench foot may for obvious reasons, aggravate and precipitate any latent occlusive disease of the arteries. Furthermore, a patient with a deficient circulation of the foot is more susceptible to trench foot. The combination of trench foot with other organic diseases of the peripheral vascular system has been encountered in several patients of this hospital. The realization that in the vast majority of patients convalescing from trench foot there is no disturbance in the pulse of the foot, in a negative way at least, is of some value in differential diagnosis.

Summary. 1. The incidence of palpable dorsalis pedis and posterior tibial pulsations in 500 soldiers convalescing from trench foot was compared with 906 infantry soldiers without circulatory complaints of the extremities. No significant difference was found.

2. Trench foot is essentially a disease involving the smaller arterioles and capillaries and only in rare instances are the larger arteries involved to the point of occlusion.

3. In a patient convalescing from trench foot an absence of both the posterior tibial and dorsalis pedis pulses on the same side should invite careful search for some other peripheral vascular problem.

REFERENCES

1. BLACKWOOD, W.: Pathology of Immersion Foot, *Brit. J. Surg.*, **31**, 329, 1944.
2. LANGE, K., and BOYD, L. J.: The Functional Pathology of Experimental Frostbite in the Prevention of Subsequent Gangrene, *Surg., Gynec. and Obst.*, **80**, 346, 1945.
3. LARREY, D. J.: *Mémoires de Chirurgie Militaire*, Paris, **3**, 60, 1812 (cited by ⁸).
4. LESSER, A.: Report on Immersion Foot Casualties From the Battle of Attu, *Ann. Surg.*, **121**, 257, 1945.
5. LEWIS, T.: (a) Observations on Some Normal and Injurious Effects of Cold Upon Skin and Underlying Tissues: Reactions to Cold, and Injury of Normal Skin (Holme Lecture), *Brit. Med. J.*, **2**, 795, 1941; (b) Observations on Some Normal and Injurious Effects of Cold Upon Skin and Underlying Tissues: Chilblains and Allied Conditions (Holme Lecture), *Brit. Med. J.*, **2**, 837, 1941; (c) Observations on Some Normal and Injurious Effects of Cold Upon Skin and Underlying Tissues: Frostbite (Holme Lecture), *Brit. Med. J.*, **2**, 869, 1941.
6. REICH, R. S.: The Pulses of the Foot: Their Value in the Diagnosis of Peripheral Circulatory Disease, *Ann. Surg.*, **99**, 613, 1934.
7. SILVERMAN, J. J.: The Incidence of Palpable Dorsalis Pedis and Posterior Tibial Pulsations in Soldiers, *Am. Heart J.* (in press).
8. SMITH, J., RITCHIE, J., and DAWSON, J.: Clinical and Experimental Observations on the Pathology of Trench Frostbite, *J. Path. and Bact.*, **20**, 160, 1915-16.
9. TALBOTT, J. H.: The Physiologic and Therapeutic Effects of Hypothermia, *New England J. Med.*, **224**, 281, 1941.

PROGRESS OF MEDICAL SCIENCE PEDIATRICS

UNDER THE CHARGE OF
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BASAL METABOLISM IN CHILDHOOD: CURRENT PROGRESS

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THE resting child releases more heat per kilogram of body weight and per square centimeter of body surface than does the adult. The excess above the adult level is greatest in infancy and diminishes more or less regularly until maturity is reached. Can it be that age, height, weight, and body surface—our ordinary standards of reference—are unsound bases for standardization, so that we must look elsewhere for more perfect measures of reference? Does this excess represent a true physiologic difference between adult and child, due to the phenomenon of growth itself? Moreover, no matter what standards are taken, wide ranges of variation are encountered from child to child. Are these variations due to lack of uniformity in the growth impulse *per se*, or to obscure other causes? These problems are of immense practical importance. Until we have the answers (and the multiplicity of studies still in progress indicates that the questions have as yet been only partially answered) we must view childhood basal metabolism as being still, in part, *terra incognita* to the clinician.

This Review summarizes the major contributions on the more controversial aspects of the subject, and the interpretations offered, as expressed in the medical literature of the past 5 years. For a good

outline of the clinical knowledge already at hand the reader is referred to the chapter on basal metabolism in childhood by Talbot^{29c} in Brennemann-McQuarrie's "Practice of Pediatrics." The monograph of Du Bois¹¹ and the various papers by Lewis and associates¹⁹⁻²² contain critical summaries of the studies on basal metabolism in childhood up to the dates of publication of these individual reports.

Vogelius³¹ too has furnished a running survey of the published reports on metabolism standards for children, his last citations being in 1939.

DEFINITION. The basal metabolism is the energy released by the living body when in absolute rest. This energy is released almost entirely in the form of heat.

The body surface area is of the greatest importance in determining the rate at which heat is lost from the warm-blooded human body. Among adults it serves excellently as a method of reference for eliminating the effect of differences in body size upon basal heat output, and most adult standards are expressed in terms of surface area. In childhood, however, as stated in the introduction, the variations are much wider, no matter whether the individuals are compared according to surface area or weight, height, age, or combinations of factors.

The heat production of any given individual at any one time is conditioned by fluctuant influences such as antecedent intake of food, physical activities, and the body temperature. To eliminate these variables the readings are customarily taken at least 12 hours after a meal when the digestive processes are quiescent, with the subject relaxed and free from mental, emotional, and physical effort, and without fever or chilling. The heat output is then considered a measure of the vegetative body functions only. Ideally the subject should be asleep, since the rate is a little lower than when awake (see below) but inasmuch as most people are not able to sleep during the test the heat output in the awake but resting state is taken by common consent as the definitive datum. Every laboratory should try to standardize its performance of the determinations, so that whatever small errors may creep in will tend to be always in the same direction. From the standpoint of the preliminary rest period, it has been demonstrated once more by Nolan,²⁵ Robertson,²⁶ and Vogelius³¹ that there is no difference between readings from subjects who have walked to a hospital in the morning before breakfast, and when the same subjects have slept overnight at the hospital and remained in bed until tested.

METHODS. Measurement of heat production by direct calorimetry required elaborate physiologic apparatus and skilled technical accuracy. For this reason indirect calorimetry is almost universally employed for such measurements. Indirect calorimetry rests on the discovery that a number of body functions such as oxygen consumption and carbon dioxide elimination run parallel, under standardized controlled conditions, to heat production. This has been well validated by comparisons with direct calorimetry. Since the oxygen consumption is the easiest to follow, clinical practice usually utilizes respiration devices which measure the amount of oxygen consumed by the patient in a given unit of time.

A survey of the operational principles and historical development of the modern apparatuses for measuring oxygen consumption has been presented by Roth and Roth.²⁷ The respiration device most widely used is of the closed circuit type, which employs a gas system linked to the subject's respiratory system, and not connected with the outside atmosphere during the period of the test. The observed rates of oxygen absorption through the lungs and into the blood portray the true rates of intracellular oxidation and therefore of heat production. Roth and Roth conclude that when properly employed such closed circuit devices are dependable and accurate. The reliability of the results depend almost exclusively upon the circumstances under which the tests are done and the coöperation and handling of the subjects. A good exposition of the technical and psychologic aspects of metabolism testing has been prepared by Lex.²³

Lewis, Iliff and Duval²⁰ made a direct comparison of an open circuit and a closed circuit method. In the open circuit method the child was placed in a sealed windowed chamber into which outside air could be piped; from the content of oxygen and carbon dioxide in the ingoing and outgoing air the respiratory quotient and the heat production was computed. These workers obtained comparable values for basal metabolism when both procedures were used in close succession with the same child on the same day. They found also that the basal metabolism was not affected by altitude, at least for elevations up to 9000 feet.

OBSERVATIONS. *Sleep.* Sleep does tend to give lowered readings. The studies of Wang and Kern,³² for example, demonstrated that sleep lowered the metabolism, by as much as 5.7 to 30.6 %, with an average of 15 %. Lewis, Kinsman and Iliff²² have summarized the many reported studies which seem to establish this principle beyond question. One criticism which has been repeatedly levelled against Talbot's^{29b} standards is that they are a little

low because they include figures from Benedict and Talbot's² original investigation in which the determinations were made on sleeping children, and the lowest obtained values were taken for the standards.

Is preliminary training of the subject necessary? Several workers^{6,12} have contended that for clinical use the standards of basal metabolism should be based solely on the first test which appears satisfactory, for the reason that this is the one customarily used in clinical practice. Lewis, Duval and Iliff¹⁰ are the most recent of many workers to take issue with this view. They contend that the first test often gives higher readings due to emotional and other causes, and furthermore that many patients are frequently subjected to repeated tests as the attending physician follows the results of treatment. To check this question by actual experience, these authors reviewed the records of their studies on children aged 2 to 10 years. Of 94 subjects, only 35 % gave satisfactory results with the first test; 55 % by the second test; 80 % by the third test. No determination was considered satisfactory from the standpoint of coöperation unless the child refrained from muscular activity and was relaxed but awake. Once the procedure was going smoothly, however, the results of subsequent satisfactory tests did not differ significantly from the results of the first satisfactory test.

Vogelius³¹ likewise found, with girls 7 to 15 years of age, that the oxygen consumption often diminished as the number of determinations was increased. He recommended therefore that enough serial determinations be done until 4 consecutive readings are obtained which no longer show any falling tendency. His average readings for the first determination were 8 % higher than the final ones secured by the method recommended. Some of the first determinations were 30 % higher than those made later.

Shock^{28a} had similarly concluded, from his study of 100 adolescent boys and girls, that "the reliability of metabolism meas-

urements is not significantly altered by repeated testing, provided a preliminary training is given."

Infants. It is in the 1st year of life that the rate of body growth is at its highest. Several recent studies throw a little more light on the metabolism in this period of rapid development. Clagett and Hathaway⁹ described repeated observations of 8 infants over a 5 to 10 month period. Six of the 8 children were twins. The open-circuit metabolism chamber method was used and the rates were measured during sleep. Comparison of the figures for twins and non-twins showed no greater similarity for the rates of the twins. The 24 hour output of calories of each infant tended to increase with growth at a relatively uniform rate, yet when the total caloric output was plotted against the separate factors of age, weight, height and surface area, wide spontaneous fluctuations became manifest. The dispersion was least when total calories were referred to age. This was not in accord with the earlier results of other workers, *e. g.*, Levine and Marples¹⁸ who had suggested that stature was probably the best standard of reference for prediction of the infant's basal rate. No sex differences were noted in Clagett and Hathaway's⁹ series, and this had also been the experience of Levine and Marples. The conclusion drawn by the authors was that no single basis of comparison is uniformly satisfactory for predicting the basal rate.

Another investigation of what goes on in the infancy period has been reported by Benjamin and Weech.⁴ These authors measured the heat output of 4 infants, 2 for as long as 14 months, using an open-circuit metabolism chamber and performing the estimates 1 to 3 times weekly. The average daily fluctuation ranged from 6 to 14 %; the coefficient of variation for 257 observations of the 4 infants came to over 9 %. In general younger infants showed larger fluctuations than those who were older. These estimates of longitudinal variability were compared with

the scatter exhibited by cross-sectional analyses of heat production in infancy as studied by other authors.^{2,18} The latter had an even higher coefficient of variation, namely 14.9%. Such variability renders it difficult to establish reliable correlations between heat production and measures of growth when the period of observations are short.

Benjamin and Weech next related heat production to different measures of growth to see which would have the highest correlation. They noted first of all that such correlations are hampered by the spontaneous erratic fluctuations of the individual children. The association between total calories and body weight was closest, without any significant change over the age period studied. The associations between total calories and both surface area and height were less marked, but with some direct relationship. The authors concluded that, while a trend to reduction in the caloric output per kilogram of body weight may proceed at a slow and almost uniform rate through infancy and childhood, the rate of this decline does not manifest an obvious relationship to the rapid changes in the rate of growth which take place during infancy.

They encountered no "kink" in the individual energy curves at the end of the 1st year of life, as has been theorized by some workers^{34b} on the basis of mean statistics derived from cross-sectional studies. They pointed out that metabolically active organs have higher rates of heat production than those less active; that the total heat given off by the body is the sum of all the individual fractions of heat derived from the separate organs and tissues; and that as the relative weights of the organs alter with advance in age the total heat production becomes correspondingly modified in a way not exactly proportional to increase in total body mass.

Children of Preschool Age. Lamb¹⁶ was able to train 8 children 2 to 4 years of age how to relax completely while being tested with the conventional mask and closed-circuit oxygen method. She determined

the basal metabolism of these children at 3 month intervals for 1 year, and compared the results with the few tables of standards already available. The subjects were healthy, 3 girls and 5 boys, attending a nursery school. Two tests were made on each morning, and repeated on successive mornings until the lowest figures obtained for calories per hour agreed within 5%. To meet this criterion, 4 to 6 tests had to be made with every child. In nearly half the tests all 4 recordings made on 2 different mornings with each subject checked within 5% of the lowest value.

The crude figures for calory utilization showed wide variations. From the calories per hour the authors computed the calories per square meter of body surface, the calories per kilogram of body weight and the calories per centimeter of height. With every child the smallest spread of the figures occurred when metabolism was expressed as calories per square meter of surface area, the maximum being about 20% above the minimum value. For calories per centimeter and per kilogram the maximums were respectively 23 and 25% above the minimums.

The data were compared with 4 sets of standards recommended for children (Benedict,³ height; Dreyer, height; Talbot,²⁹ height and weight). The extremes ranged from +31% with 1 boy with the Talbot weight standard to -20.1% with another boy with the Dreyer standard. The greatest differences were between the Benedict height and the Dreyer standard. Dreyer's was the only formula for a standard which gave a consistently negative deviation. The author commented that these discrepancies emphasize the need for more accurate standard for children. Other reports on basal metabolism of healthy normal children, in this age period also show negative deviations from the formula of Dreyer and positive deviations from the standards developed by Benedict and Talbot.

In conclusion Lamb suggested that probably various stages of maturation

exist in children of the same chronologic age, and that basal metabolism is related to the rate and extent of maturation. Basal metabolism values for children therefore cannot be compared successfully on the basis of chronologic age alone; the basis must allow also for the developmental progress. Standards must incorporate such allowances.

Childhood Period. The results of careful studies on basal metabolism in children between 2 and 12 years of age in Denver were summarized in 1937 by Lewis, Kinsman and Iliff²² and again in 1943 by Lewis, Duval and Iliff^{19a,b} in carefully documented reports.

The children studied by Lewis, Kinsman and Iliff were normal. There were 718 satisfactory tests of 57 girls and 1007 satisfactory tests of 70 boys. They were between 2 and 12 years of age when tested. The determinations were made by the open circuit chamber method. The data for the boys and the girls were tabulated separately, and then the caloric outputs per hour were computed according to the body characteristics of age, weight, height and body surface, and also for the other characteristics as related to age. The scatter about the means for all of these bases of computation was about the same, except that height showed a greater dispersion. From meticulous comparisons of their data with the figures from other sources they conclude that the range of normal variation may extend approximately $\pm 17\%$ from their own values. Reported values lower than this range of variation may be explained by the subjects having been asleep during the tests, and higher results may have been due to different experimental conditions. They concluded that when the caloric output per hour is calculated for any single subject by the different methods of referring the heat production, the figures obtained will vary from the normal to approximately the same degree regardless of the method, *provided* the height and weight of the child, and hence his body surface, are close to the means for normal children

in his age group. In other words, with well-proportioned children the physician may use any one of the three sets of central trend line values which showed the lowest coefficients of variation: calories per hour per square meter referred to age, calories per hour referred to weight, or calories per hour referred to body surface. On the other hand, with children whose measurements fall outside the range of the children who were used as subjects for the standards, the rates obtained by the different methods of referring the metabolism may differ considerably one from another. A further collection of data is needed, with a comparative study of the anthropometric measurements and basal metabolism findings. Until such a correlated study has been made the authors recommend that all three sets of the standards mentioned above be given consideration in judging the status of such patients.

In their reports the standards are presented according to calories per hour per square meter referred to age, and calories per hour referred to surface area, weight, and height, respectively, because dispersion was least with these methods of reference. Calories per hour in terms of height had a somewhat high variation, but the values are included because this method of reference has been widely used by other workers. Their paper contains, in addition, graphs which compare their standards with those of recognized authorities in the field, such as de Bruin,¹⁰ Talbot,^{20a,b} Bierring,⁵ Boothby, Berkson and Dunn,⁶ Miana-Calabrese,²⁴ and Webster, Harrington and Wright.³³ The trends for all are much the same, though the values from these various studies do not coincide precisely.

The standards are given as average or mean values. The authors have calculated the various coefficients of variation: 95% of their healthy children fell within $\pm 12\%$ of the standards when calories per hour were referred to weight or surface area, and when calories per hour per square meter were referred to age; 99.7% of nor-

mal children fell within $\pm 18\%$ of these standards.

Adolescence. Among the older authorities there is considerable disagreement over whether a positive increase in the relative heat production takes place at the time of puberty. Göttsche,¹³ Lax and Petényi,¹⁷ Topper and Mulier,³⁰ and Kestner and Knipping,¹⁵ for example, have described a rise, whereas Boothby and Sandiford,⁷ Bailey,¹ and Bierring⁵ failed to substantiate it. All of these workers employed the method of group sampling at different age periods. Webster, Harrington and Wright³³ in 1941 attacked the problem from a different aspect, reporting on longitudinal observations of one group of children over a 6 year period. They measured at approximately 4 month intervals the basal metabolism of 13 boys and 8 girls in rural New York state, commencing at age 10. The closed-circuit method was employed and the reports were expressed in terms of surface area. In the period of preliminary training nearly all the children displayed a sharp decrease in readings. From then on, however, only rarely was there a striking variation between one observation and the next. With both the boys and the girls the deviations of the individual readings from the mean curves were not marked.

In accord with the experience of all previous observers the basal metabolism for the boys was higher than that for the girls. There was a gradual decline in the basal metabolism (calories per square meter of body surface per hour) over the age period 10 to 16 years for both boys and girls. This was most striking between ages 11 and 12 years. The closest conformity was with the Bierring standards for boys and the Kestner and Knipping standards for girls. The onset of menses produced no significant change in heat production. For the boys the total output of calories per 24 hours rose progressively over the entire period, parallel with growth in height and weight. For the girls this was true until the mean age of $14\frac{1}{2}$ years, above which the rate of increase in

total calories became much less marked. This coincided with a fall in the body weight curve and a flattening of the curve for increase in height.

Lewis, Duval and Iliff^{19a,b} have also presented some figures on normal children 13 to 15 years old, inclusive. In general, the lowest degrees of scatter were encountered when the results were expressed in terms of the same characteristics they found most satisfactory for younger children. (See discussion in preceding section.) A detailed comparison is given between their mean values and similar data reported by other workers. Many of the other reported standards fall within $\pm 5\%$ of the mean values of this study. The authors comment that no explanation is at hand for the relatively high values for adolescent girls reported by Topper and Mulier.³⁰

Shock^{28a} carefully carried out repeated measurements of basal metabolism by the Tissot open-circuit technique on a group of 50 adolescent boys and 50 adolescent girls. He was desirous of determining which measure of growth could serve as a basis of reference, and attacked the problem by noting which of the body properties for normal subjects of a given sex and age gave the smallest range of values in the readings. Determinations were made in triplicate on each of 2 successive days every 6 months over the age interval 11.5 to 18 years. Calculated for both boys and girls at each age level were the coefficients of variation for (a) calories per square meter per hour, (b) calories per kilogram per hour, (c) cubic centimeters of oxygen consumed per square meter per minute, (d) cubic centimeters of oxygen consumed per minute and (e) total cubic centimeters of oxygen per kilogram per minute. Coefficients of variation were consistently lower for calories per square meter per hour and for cubic centimeters of oxygen consumed per square meter per minute than for similar values expressed per kilogram of body weight. His results, therefore, were expressed in terms of cubic centimeters of oxygen consumed per square

meter per minute and of calories of heat produced per square meter per hour.

Shock compared his data with other reports and found, strikingly, that the differences in average metabolism values in reports of different observers were greater than the average age trends shown during adolescence in any single study. "It seems that careful standardization of techniques is as important in the interpretation of the results of metabolism tests as is the question of the chronologic age of the subjects."

Shock's analysis brought to light also that the range of values for basal metabolism which will include 95% of a normal population at any given age between 11.5 and 17.5 years is greater than the average change in metabolism with growth over the adolescent period. A deviation of $\pm 15\%$ from the mean will include approximately 95% of normal children but a deviation of $\pm 20\%$ from the mean value is necessary to include 99% of them within this age range. The conventional limits for normalcy of $\pm 10\%$ deviation from the mean value are, therefore, too narrow; they should be extended to at least $\pm 15\%$ if norms expressed in terms of chronologic age are to be used.

The question of the effect of menarche on basal metabolism of adolescent girls was also reexplored by Shock,^{28b} who determined the basal metabolism of 50 California girls at 6 months intervals, starting at age 11 and continuing for 6 years. Careful notes of the menstrual phenomena were coincidentally made. He tabulated the respective ages as months before or after menarche, instead of as chronologic age. The basal oxygen consumptions were calculated in relation to surface area, which in turn was computed from height and weight. It was found that a sudden rapid fall in basal oxygen consumption took place with the beginning of menstruation, or 6 to 12 months earlier. The mean curve which was approximately 41 calories per square meter per hour up to menarche had fallen to approximately 35 calories per square meter per hour 24 months later, and

then continued to fall, but more slowly, until the full adult level was reached. The phenomenon was interpreted as another aspect of maturity, rather than a consequence of endocrine changes associated with menstruation. With reference to the possible existence of a prepubertal rise in basal oxygen consumption the author commented that his observations did not begin at an early enough chronologic age to answer that question with assurance, though many of the individual girls, especially those who menstruated late, seemed to have such a prepubertal rise.

Johnston¹⁴ described observations of basal metabolism and calcium and nitrogen balance in 6 tubercular adolescent girls studied over 9 day periods for 300 continuous days. In these girls sexual maturation was accompanied by a decrease in the calcium and nitrogen retentions. There was first a physiologic rise in basal metabolism, followed by a fall at about the menarche. Johnston suggested that the metabolic retentions paralleled the metabolic rate, apparently as a phenomenon of growth. He cited several other girls in whom the premenarcheal rise in basal metabolism was accompanied by toxic manifestations of hyperthyroidism. These girls were given iodine therapy and rest in bed, and a prompt fall in the metabolic rate occurred at the onset of the menses. He recommended that small doses of desiccated thyroid be given if the depressed phase of the metabolism cycle should reach a pathologically low level.

Vogelius³¹ was interested in exploring more adequately than hitherto achieved the problems involved in setting up basal metabolism standards for girls aged 7 to 15 years. He accordingly analyzed 1150 tests with 150 normal Danish girls, and a smaller number of tests with children obese, dwarfed, or suffering from other disorders of metabolism. He also reviewed critically the reports from other workers, notably that of Bierring⁵ on Danish boys.

When doing the basal metabolism tests the following data were obtained for each

subject: age, oxygen consumption, weight, height, and surface area computed according to Du Bois' "linear formula." He made a careful statistical investigation of these various data, utilizing a new mathematical approach—that of "stepwise confluence analysis." If the observations were divided into two age ranges, namely 7 to 15 years and 16 to 18 years, the exact age within these ranges could be ignored. Basal metabolism seemed best characterized by formulas built up to include oxygen consumption, surface area, weight and height. Inasmuch as these computations are highly involved, one can get along on a simpler basis using weight as the basis of reference, provided the girls are normal with respect to weight-height ratio. The author provides 2 monographs for the evaluation of the ratios of metabolism-weight and weight-height. He provides also a table of metabolism standards for girls aged 7 to 15 years, in which the data are given as calories per 24 hours for body weights from 15 to 75 kg. The table gives not only standard values but also the lower and upper 95 % limits. These standards do not fit subjects who may be obese, dwarfed, or otherwise abnormal in the height-weight ratios given.

Vogelius is highly critical of the common practice of expressing the metabolism in terms of per unit of weight or per unit of surface area in relation to age. For one thing, each of these variables already reflects growth changes due to age over the years up to age 16. For another, as illustrated by examples from data of other workers, differences in weight or surface area become carried over with undue emphasis into the final results. Furthermore, the problem of comparison of standards is not solved, since no pair of standards proposed by different workers run exactly parallel. Clearly the information at hand for evaluation of all the factors which determine the basal metabolism is not wholly complete.

Brown and Wasson⁸ reported 154 tests of basal metabolism performed on 97 ambulant children ill with rheumatic fever.

They used the closed circuit method and derived their calculations from the height-weight (or surface area) standard of Boothby and Sandiford.⁴ The age distribution of the children was not reported, and there is no statement whether preliminary training was given. The mean of the rates was 7.6 %. Forty-three children had at least 1 reading below 10 %. Of 33 children who had more than 1 test, 21 gave lower readings in the second tests which were performed during the spring.

Diagnosis of Hypothyroidism. Wilkins and Fleischmann³⁵ judge the determination of the basal metabolic rate to be of little aid in diagnosing hypothyroidism in childhood. They found that slight emotional disturbances can accelerate the rate for long periods, and this may not be detected by the observer. Younger children and mentally defective children usually do not coöperate well. In fact in only 1 of every 4 children with hypothyroidism studied by Wilkins, Fleischmann and Block³⁶ could satisfactory determinations be obtained. Furthermore, even when the performance of the tests is satisfactory, the selection of a proper standard for comparison becomes difficult. If the hypothyroid child is dwarfed, inadequate standards are available; if he is obese the low oxygen consumption of adipose tissue gives rise to abnormally low figures when referred to surface area standards. With the surface area standards the results of tests of obese children with no signs of hypothyroidism may be as low as -25 to -40 %. With the Talbot height standards obese children without hypothyroidism usually have rates which are normal or even elevated, whereas hypothyroid children have rates which are low. Yet occasional children have been seen whose rates have been low with the height standards but without signs or symptoms of thyroid deficiency. To avoid error, therefore, the diagnosis of hypothyroidism must not be made on the basis of a low metabolic rate alone. Other abnormalities such as sluggishness and hypercholesterolemia must be associated.

Influence of Growth. Wetzel³⁴ has emphasized that growth in the biologic world seems to follow certain well-established dynamic principles which are expressible in mathematical terms. Complex equations may be derived which can be applied equally to the phenomenon of growth as it is operative in tadpole tails, yeast cultures, tissue cultures, oxygen consumption of the fertilized egg of *Echinus* and heat production of the chick embryo. Human basal heat production as measured by authorities such as Benedict and Talbot² can also be shown to conform rather closely to these theoretical trends. Growth is an integral part of these equations, and is one element in determining the heat production and oxygen consumption of the human child. However, within the span of relatively short periods of time, such as 1 or 2 years, the changes in the metabolism due to changes in intensity of the growth impulse are much smaller than the variability of the individual measurements, and for that reason escape detection.

Wetzel has devised an intricate growth chart, known as a "grid," for portraying and appraising the growth and development of children. With this chart one first plots weight against height to obtain the "development level," and then plots this value against age to ascertain the "schedule of development." For a full exposition the reader is referred to the original presentations.³⁴ The grid chart contains a scale for estimating basal metabolism of boys and girls directly from the horizontal extensions of the level lines without further correction for "off-size," age, or body build. The exact manner in which this scale of basal metabolism values has been built up is not obvious from the text. When evaluating the basal metabolism of any child, one measures the heat production in the usual manner and then compares it with the printed estimate of what a normal child's metabolism of the same height and weight should be. When the measurements are carefully done and sufficiently repeated, "observed values in children otherwise known to be healthy

will frequently not differ from the grid standards by more than $\pm 7\%$." The factors of age and physique do not need to be considered, according to this author, because growth, and not chronologic age, is the conditioning factor. He argues further that not all of a subject's height and weight is involved in heat output but only "that portion of each of these 2 measures of size which, in combination with the other, yields the component of development." The technique is said to work equally well with obese children inasmuch as the factor of physique is not incorporated into the calculations.

The recognized authorities in the field concede that Wetzel's approach to the relationship between growth and metabolism may be original and provocative, and helpful with many individual cases. They feel, however, that this approach is not yet the complete answer to the problems of just how the influence of growth upon metabolism can be measured and why so wide a range of basal readings is met with among children who appear to be similar with regard to the various measures of growth.

Summary. Many tables for the resting oxygen consumption of normal children have been gathered to serve for the evaluation of the status of other individual children. These standards are expressed customarily in terms of units of age, or height, or weight, or surface area, or of several of these growth measures in combination. Age is the least satisfactory as a direct basis of reference. There is no universal agreement as to whether height, or weight, or surface area, with or without reference to age, work out the best in actual practice.

With children of average or normal body build any of the different types of standards seems to work well. But when the body build is atypical or distorted, as, for example, with obese children or dwarfs, the different standards give results which fail to conform one with another.

The normal range for individual varia-

tion is greater in childhood than in adult life. One reason for this appears to be the growth impulse, which stimulates the metabolism to an as yet unmeasured degree. Obviously, we must work out more fully the importance of growth, and of the thyroid gland, and of other con-

trolling factors now only guessed at. Until then the physiologic significance of basal metabolism measurements in childhood must remain obscure and of little clinical value in the presence of prominent deviations from the patterns of most normal children.

REFERENCES

- (1.) Bailey, C.: Hawk and Bergeim, *Practical Physiological Chemistry*, 9th ed., Appendix, p. 896, Philadelphia, Blakiston, 1926.
- (2.) Benedict, F. G., and Talbot, F. B.: Carnegie Inst., Washington, Publ., (a) No. 233, 1915; (b) No. 302, 1921.
- (3.) Benedict, F. G.: *Proc. Nat. Acad. Sci.*, 6, 7, 1920.
- (4.) Benjamin, J. R., and Weech, A. A.: *Am. J. Dis. Child.*, 65, 1, 1943.
- (5.) Bierring, E.: *Standard Metabolism of Boys*, Copenhagen, Levin & Munksgaard, 1931.
- (6.) Boothby, W. M., Berkson, J. B., and Dunn, H. L.: *Am. J. Physiol.*, 116, 468, 1936.
- (7.) Boothby, W. M., and Sandiford, I.: *Am. J. Physiol.*, 90, 290, 1929.
- (8.) Brown, E. E., and Wasson, V. P.: *J. Pediat.*, 23, 19, 1943.
- (9.) Clagett, D. D., and Hathaway, M. L.: *Am. J. Dis. Child.*, 62, 967, 1941.
- (10.) de Bruin, M.: *Am. J. Dis. Child.*, 57, 29, 1939.
- (11.) Du Bois, E. F.: *Basal Metabolism in Health and Disease*, Philadelphia, Lea & Febiger, Chap. 8, 1936.
- (12.) Eaton, A. G.: *J. Lab. and Clin. Med.*, 24, 1255, 1939.
- (13.) Göttche, O.: *Monatschr. f. Kinderh.*, 32, 22, 1926.
- (14.) Johnston, J. A.: *Am. J. Dis. Child.*, 59, 287, 1940.
- (15.) Kestner, O., and Knipping, W. H.: *Die Ernährung des Menschen*, 3rd ed., Berlin, Springer, 1928.
- (16.) Lamb, M. W.: *Am. J. Dis. Child.*, 70, 220, 1945.
- (17.) Lax, H., and Petényi, G.: *Monatschr. f. Kinderh.*, 36, 381, 1927.
- (18.) Levine, S. Z., and Marples, E.: *Am. J. Dis. Child.*, 41, 1332, 1931.
- (19.) Lewis, R. C., Duval, A. M., and Iliff, A.: (a) *Am. J. Dis. Child.*, 65, 834, 1943; (b) *J. Pediat.*, 23, 1, 1943; (c) *Am. J. Physiol.*, 140, 461, 1944.
- (20.) Lewis, R. C., Iliff, A., and Duval, A. M.: *J. Lab. and Clin. Med.*, 28, 1238, 1943.
- (21.) Lewis, R. C., Iliff, A., Duval, A. M., and Kinsman, G. M.: *J. Lab. and Clin. Med.*, 28, 851, 1943.
- (22.) Lewis, R. C., Kinsman, G. M., and Iliff, A.: *Am. J. Dis. Child.*, 53, 348, 1937.
- (23.) Lex, J. K.: *Metabolism Manual*, Baltimore, Waverly Press, 1943.
- (24.) Miana-Calabrese, D., and Pemelli, S.: *Quad. Nutrizione*, 4, 393, 1937.
- (25.) Nolan, L. E.: *Am. J. Clin. Path.*, 13, 278, 1943.
- (26.) Robertson, M. D.: *Brit. Med. J.*, 1, 617, 1944.
- (27.) Roth, P., and Roth, H. P.: *Medical Physics*, Chicago, Year Book Publ., p. 718, 1944.
- (28.) Shock, N. W.: (a) *Am. J. Dis. Child.*, 64, 19, 1942; (b) *Am. J. Physiol.*, 139, 288, 1943.
- (29.) Talbot, F. B.: *Am. J. Dis. Child.*, (a) 21, 519, 1921; (b) 55, 455, 1938; (c) *Brennemann-McQuarrie System of Pediatrics*, Hagerstown, Md., Prior, Chap. 22, 1945.
- (30.) Topper, A., and Mulier, H.: *Am. J. Dis. Child.*, 43, 327, 1932.
- (31.) Vogelius, H.: *Acta med. Scandinav.*, Suppl. 165, 1945.
- (32.) Wang, C. C., and Kern, R.: *Am. J. Dis. Child.*, 36, 83, 1928.
- (33.) Webster, B., Harrington, H., and Wright, L. M.: *J. Pediat.*, 19, 347, 1941.
- (34.) Wetzel, N. C.: (a) *J. Pediat.*, 22, 82, 208, 329, 1943; (b) *Medical Physics*, Chicago, Year Book Publ., p. 513, 1944.
- (35.) Wilkins, L., and Fleischmann, W.: *J. Am. Med. Assn.*, 116, 2459, 1941.
- (36.) Wilkins, L., Fleischmann, W., and Block, W.: *J. Clin. Endocrinol.*, 1, 3, 1941.

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PUERPERAL INFECTION

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PUERPERAL infection is referred to as puerperal fever, puerperal sepsis, and child-bed fever.

HISTORICAL. Excellent descriptions of cases of puerperal infection were written by Hippocrates (400 B.C.) and other early writers and references to it throughout the Middle Ages are numerous.¹⁷ It was not until the advent of hospitals in the 17th century, however, that the disease became epidemic in nature. During this period when nothing was known about contagion, extremely high mortalities resulted from puerperal infection. White⁷⁶ (1773), and Gordon²⁶ (1795) did much to help establish the principles of cleanliness, disinfection and segregation. Holmes³⁶ in 1843 published his famous paper "The Contagiousness of Puerperal Fever," in which he proved that the disease was transmitted directly or indirectly from 1 individual to another. Semmelweis⁶⁶ (1847) showed unequivocally that puerperal fever is an infection of the genital tract and indicated the correct manner of its prevention. In 1879 Pasteur⁵⁹ demonstrated the presence of streptococci in the blood of a puerperal sepsis patient both before and after her death. From that date every form of puerperal sepsis was attributed to this agent, until later research clearly demonstrated that there is no specific organism for puerperal infection.

SOURCE OF INFECTION. Puerperal infection arises from the genital tract and is most frequently acquired just before, dur-

ing, or soon after delivery. Parturition causes many wounds in the birth canal that may serve as portals of entry for microorganisms; but the chief factor in the etiology of puerperal infection is the carrier who directly or indirectly transmits virulent bacteria to the birth passages.

Infectious spray from the nose or throat of those in attendance is a well-established source of contamination.^{12,51,58,67,73} Williams⁷⁷ has shown definitely that the curve of the incidence of puerperal infection follows the curve of the incidence of respiratory infection, but at a somewhat later date Smith⁶⁷ and Colebrook¹² have shown that the parturient can be infected by secretions of her own mouth and nose. Fingering of the vulva and vagina by the patient before, during and after labor is a source of infection. Horn,³⁷ Von Buben,⁷ and Liubimowa⁴⁵ have emphasized the danger of infection following coitus before or early in labor. Vaginal douches before, during or after labor have been associated with puerperal infection. Any break in aseptic technique in spontaneous or instrumental delivery, catheterization and postpartum care of the vulva, and inadequate sterilization of a common bed-pan and other sick-room accessories are all sources of contamination.⁴

Many investigators^{46,69,78} have studied the bacterial content of the vagina and cervix, and a multitude of various microorganisms have been cultured from the

cervix during pregnancy and many conclusions have been reached. Some of these organisms are morphologically and culturally identical with bacteria which initiate pathologic changes, although the incidence of such organisms varies greatly in the reports of different observers. In Conti's¹⁵ study (1941), streptococci were obtained in cultures from 14.5% of his patients, and in 3.3% the bacteria were hemolytic. He found that morbidity was somewhat higher in patients in whom the cervix harbored streptococci, especially if these organisms promote hemolysis. He believes endogenous infection from the cervix does occur, but in his series was exceedingly mild and of short duration. Bumm and Sigwart⁹ concluded from their study that there was no definite relationship between streptococci cultured from cervixes during the antepartum period and puerperal morbidity. Douglas and Davis's²⁰ study of 1000 patients indicates that the great majority of infections occurring during the puerperium and post-abort period were endogenous in origin, and caused for the most part by different groups of non-hemolytic streptococci. The organisms they considered exogenous in origin were the hemolytic streptococcus, *Staph. aureus*, pneumococcus, and other pyogenic organisms not usually found in the cervix or vagina. These, they believe, were brought to the genital tract by the patient or her attendants. The second group of exogenous organisms included the gram-positive bacilli, *Cl. welchii*, and some strains of streptococci whose normal habitat is in the gastro-intestinal tract. These organisms, they believe, were introduced into the genital tract during various diagnostic and therapeutic procedures. Williams⁷⁸ states that while bacteriologic research affords a certain amount of evidence of autoinfection, clinical observation speaks against it. Kulka⁴³ found that a bacteremia existed in 18% of women during normal afebrile labors and puerperia. The organisms usually found in the blood were the colon bacillus, the *Strep. hemolyticus* and staphylococci. On the 3rd day

after delivery, all blood cultures were negative in his study.

BACTERIOLOGY. One of the most valuable additions to our knowledge of puerperal infections during recent years is a more exact appreciation of its bacteriology and morbid anatomy. Modern serologic techniques have resulted in the separation of various bacterial species into groups, types and sub-types which are of great value in making an adequate diagnosis. Unfortunately, even with present-day knowledge of serologic type, at their disposal, the bacteriologists cannot sort out and segregate the "dangerous carriers" by the nature of the microorganism they harbor.²

The organisms most often identified in the severe and fatal infections are the hemolytic streptococcus, the anaërobic streptococcus, *Staph. aureus* and *Clostridium welchii*.³⁴ Also, *Strep. pyogenes*, *Staph. citreus* and *albus*, *Neisseria gonorrhææ*, *Diplococcus pneumoniae*, *B. coli*, *B. diphtheriæ*, *B. pyocyaneus* have been asserted to be causative factors. The common pyogenic organisms are most frequently responsible. *Strep. pyogenes*, hemolytic and non-hemolytic, as well as anaërobic and aërobic streptococci are the commonest invaders, and have been shown to be present in the uterus, or in the blood stream, in about 75% of all infected patients.^{30, 64} All known organisms, both pathogenic and non-pathogenic, have been identified with the disease. The virulence of the organism responsible for the infection seems important. Present-day knowledge of "virulence" in most cases is but little advanced from that of Weigert,⁷⁵ who in 1875 asked whether the "something" that renders a microorganism virulent is a vital bacterial product of merely "something" attached to the microorganism. Goodall²⁵ states that virulence as a property of microbes is a more or less fixed quantity, and that virulence varies in each infected patient with the natural resistance or lack of resistance of the individual.

The frequent demonstration of strepto-

cocci and staphylococci in the genital secretions gave rise to the assumption by Koller,⁴² that the mere presence of these organisms was not sufficient to explain the pathogenesis of puerperal infection. When the virulence of the bacteria of the genital secretions was determined, it was found that after spontaneous deliveries the incidence of temperature increases was not higher in the patients in whom the virulence of the bacteria was high than in those in which it was low. However, after operative terminations of birth in the presence of virulent vaginal bacteria, the inflammatory complications were frequent and prolonged. Watson⁷⁴ presents data suggesting that there are 2 main types of puerperal infection, 1 caused by a virulent strain of an aërobic hemolytic streptococcus and the other by an anaërobic streptococcus.

Bacterial synergism may account for some cases of severe puerperal infection. It has been demonstrated by Steinhorn⁶⁹ that the virulence of anaërobic streptococci is markedly increased by their association with a strain of *Staph. albus*, so that such mixtures are highly invasive for white mice. Weinberg and later Morosova⁵⁴ have called attention to the fact that when an anaërobic infection (*B. welchii*) even of the slightest degree, is associated with *B. coli* infection, the virulence of the anaërobic organism is greatly increased. Colebrook and Hare¹⁰ present data to suggest that there are, in all probability, several distinct types of anaërobic streptococci.

MORBID ANATOMY. Puerperal infection begins as a local septic infection in the soft tissues of the birth canal. The resulting inflammatory process may remain local, or may extend by metastasis to other parts of the body. Local lesions may be limited to any structure in the birth canal or may involve the entire birth passages and the adjacent tissues of the parametria and peritoneum.⁴

Tears in the vulva and vagina, when infected, may react as do similarly infected wounds in other parts of the body.

The surrounding tissues are swollen, red and painful, and there is usually a purulent and foul smelling discharge.

When the uterus is infected, the condition is known as endometritis. In mild cases where the infection is believed limited to the basal layer of the decidua, it is often spoken of as deciduitis. The severity of the uterine infection varies with the type and virulence of the invading bacteria, and the adequacy of the maternal defensive mechanism. The less virulent organisms tend to remain confined to the endometrium and produce an area of necrosis and decidual débris. A more virulent organism or a diminished defensive reaction may lead to a rapid invasion of the blood stream, or lymphatic extension to the myometrium, parametrium and peritoneum, without much alteration in the endometrium.

An infection of the myometrium may or may not precede or accompany parametritis. A protective wall of leukocytes⁸ beneath the endometrium usually protects the uterine musculature from direct invasion, but at times this may prove inadequate to prevent local abscess formation.⁶³

Infection that spreads through the lymphatics beyond the uterus may be checked in the pelvic cellular tissue. In this event, a pelvic cellulitis develops. The tissues of the parametria become swollen by a serous effusion. This may remain as a gradually subsiding cellulitis which resolves by itself; it may develop into a hard induration extending to the lateral pelvic walls which may last for months; or it may become localized into an abscess cavity, which may extend outward to the wall of the pelvis and then upward between the peritoneum and the abdominal wall in the region of Poupert's ligament, or it may follow the course of the uterine vessels to the pelvic brim and point above the crest of the ilium.

Extension of the infection through the lymphatics to the peritoneum may take place early or late in the course of a puerperal infection, and when it does occur, it is more frequently the last step in the

sequence of events which includes endometritis and parametritis. When the peritoneum is invaded, Nature attempts to wall off the infection and limit it to the pelvis by the formation of adhesions between the sigmoid, cecum, bladder and omentum. General peritonitis results if this effort is not successful.

The tubes and ovaries may participate in an extensive puerperal infection, or a perisalpingitis and perioöphoritis may follow in the course of a pelvic peritonitis.

If the thrombi which are normally present in the uterine sinuses following delivery become infected, the surrounding vessel walls show evidence of phlebitis. As these thrombi disintegrate new thrombi are formed, and extension of the inflammatory process continues in the vessel walls. If the thrombophlebitis is limited to the uterine wall, the inflammatory process may subside or local abscess formation may occur. The process may extend outside the uterus to the iliac and femoral veins.

Thrombophlebitis may lead to metastatic lesions, the most frequent of which are found in the lungs, and give rise to *many complications of that organ*. Bacterial emboli may pass through the lungs and cause acute endocarditis and other distant inflammatory lesions.

If the infection is gonorrheal in origin, it usually extends to the uterus from a previously quiescent infection of the cervix or lower birth passages. It advances by continuity along the surface of the structures involved and results in a typical gonococcal salpingitis. Mengert⁵² emphasizes the slow growth of the gonococcus and the delayed involvement of the Fallopian tubes. A local pelvic peritonitis may result from the discharge of purulent material from the tubal lumina.

DIAGNOSIS. Any postpartum patient with a temperature rise of 100.4° F. on any 2 days, exclusive of the 1st 24 hours, is considered morbid, and her fever is considered to be pelvic in origin until proven otherwise. It should be kept in mind that other infectious processes may

coëxist with a genital infection, and that the organism may be the same in both processes. A sustained temperature curve without the usual morning remissions indicates a widespread infection.

The pulse rate is an excellent indicator of the course of the disease, especially when the temperature begins to be brought under control. It should be evaluated in the light of hemorrhage and recent hemoglobin and hematocrit readings.

The patient's reaction to infection will vary with the site of infection, and with the virulence of the organism. As a rule, the systemic reaction is slight with vulvar, vaginal and minimal decidual infections, as long as drainage is good. With the spread of infection the patient's feeling of well-being leaves her, and she may complain of headache, loss of appetite, fatigue, sleeplessness and chilliness. Tenderness and pain in the pelvis are often early reliable symptoms of beginning invasion of the parametria. The gravity of the patient's condition is indicated by the degree of temperature, the character and rate of the pulse and respiration, the *change in the leukocyte and red blood cell count*, and blood and cervical culture.

Abdominal examination may reveal an enlarged, soft, and tender uterus which usually is present in cases of endometritis. When pressure on the abdomen causes pain, and rebound pain is elicited, one should consider peritonitis a definite possibility. Rectal examination may reveal a hard, unyielding, sensitive induration of the parametria which may extend out from the uterus on one or both sides to the pelvic walls. This induration restricts the mobility of the cervix.

Inspection of the vulva often will reveal the presence of infected perineal lacerations or episiotomy wounds.

Vaginal examinations are generally contraindicated in that they may be followed by extension of the infection. However, when there is good reason to believe that further information must be obtained, vaginal examination should be done with

great gentleness and under aseptic precautions. The examination should be limited to determining whether or not there is a mass in the broad ligaments and whether or not that mass is fluctuant.

As to differential diagnosis, one must distinguish most frequently between a genital tract infection and pyelitis. We have discarded the idea that a slight rise in temperature the 3rd day postpartum is "milk fever." More likely it is a mild deciduitis. Upper respiratory and throat infections must be kept constantly in mind and the possibility of autoinoculation appreciated. Pneumonia must be considered, especially in those patients who received inhalation anesthesia at delivery. Appendicitis and malaria are seen infrequently in the puerperium.

PROGNOSIS. As long as the inflammatory process is localized to the vulva, vagina, and endometrium the prognosis is favorable. An endometritis with profuse foul lochia is considered a less dangerous infection than when the lochia are less foul and scant. The prognosis becomes less favorable as the infection spreads. Extension to the parametria is serious but usually can be treated successfully. As long as peritonitis is limited to the pelvis ultimate recovery may be expected, but sterility and a prolonged convalescence often follow. Thrombophlebitis may prove fatal. The possibility of pulmonary embolism is always present with thrombophlebitis. General peritonitis and bacteriemia carry a poor prognosis.

TREATMENT. Since pyogenic bacteria are responsible for puerperal infections, protecting the genital tract from contamination is the most important phase of treatment. The vaginal secretions are protective in nature, and if given sufficient time will render innocuous most bacteria that gain access to the birth canal. To realize the maximum benefit from this natural barrier, vaginal douches and sexual intercourse must be absolutely avoided during the latter months of pregnancy. Showers rather than tub baths should be used.

All foci of infection should be eliminated as early in pregnancy as possible. This is true especially in case of infections of the external genitalia, regardless of how slight they may appear. Vulvovaginitis and gonorrhea should be treated during pregnancy, but cervical erosions and lacerations are probably best treated by being left alone.

The general condition of the patient is becoming ever more important in the prevention and treatment of infection. A diet adequate in proteins, minerals and vitamins,⁵⁶ sufficient rest, and outdoor recreation are measures of importance. The correction of anemia during pregnancy is obtained by proper diet, iron, and liver extract. The routine administration of iron is widespread, and there is a growing tendency also to prescribe liver extract during pregnancy.

The problem of developing immunity and of increasing natural resistance have not been solved, and there seems to be very little that one can do in this direction other than to recommend general hygienic measures. Specific immunization has been tried, but its value has not been proved. Adair and Hac¹ immunized over 1100 patients against streptococci, but the postpartum febrile morbidity rate of these patients was not better than the morbidity rate of non-immunized individuals. Bernstein and Otten⁵ vaccinated 51 patients with suitable vaccine with a puerperal morbidity of 5.9%. Evidence obtained by Colebrook suggests that anti-streptococcus serum may have an unfavorable effect on puerperal infections.¹¹

Youth is a great ally in combating infection, and according to Eastman²¹ the incidence of puerperal infection is no greater in mothers who have their babies close together (12 to 24 months interval) than in those who have their babies after longer intervals. Whatever advantage is gained by a rest period of several years between births seems to be offset by the factor of increased age.

LABOR. It is now well recognized that the safest place to conduct labor from

the point of view of infection is in a well-managed maternity hospital. Stout's⁷⁰ study showed the incidence of puerperal infection to be almost twice as great in a series of normal women delivered at home as in a comparable group delivered in the hospital. No difference in the severity of the infection could be detected between the 2 groups.

On entering the labor floor, after being evaluated by a physician, the first thing a patient should receive is an enema which thoroughly empties the bowel. The suprapubic and vulvar regions are shaved, and in many maternity hospitals a shower bath is given if the patient is not clean. The progress of labor should be followed by infrequent rectal examinations, and should a vaginal examination be indicated, it must be preceded by proper preparation of the vulva and the hands of the physician as is done for the actual delivery.

The literature would seem to indicate that the instillation of antiseptic solution into the vagina leads to a lower morbidity rate.^{6,50,51} Mercurochrome is employed most frequently but many other substances, including zepherin chloride and acriflavine in glycerin, are also used. Many obstetricians do not consider such treatment necessary, feeling that any invasion of the lower birth canal increases the chances for contamination. Douglas and Davis believe that the logical approach to endogenous infections is the introduction of antiseptic or germicidal agents into the vagina during labor.²⁰

Adequate sedative during labor, and especially during prolonged labor, is necessary to avoid exhausting the patient at delivery. There is no one method for the relief of pain and conservation of the patient's energy, but many reliable methods of sedation are well known and widely used.

The high incidence of puerperal morbidity following postpartum hemorrhage is well known.^{3,41} Pastore⁶⁰ points out that the mismanagement of the third stage of labor is responsible for the majority of these hemorrhages. In the non-bleeding

third stage, the management consists largely of watchful waiting until the signs of placental separation are present. After the separation of the placenta, the uterus is massaged until it contracts, then the placenta may be expressed artificially with safety. The uterus should be held for 1 hour by a reliable attendant. Oxytoxic drugs are valuable in preventing and controlling hemorrhage. Posterior pituitary extract has a rapid and vigorous action on the uterus while ergonovine has a rapid and more lasting effect. An ice-bag over the fundus also has an oxytoxic effect.

Laceration of the perineum and vagina should be aseptically repaired immediately. Postpartum care of the vulva should be similar to the case of any open or potentially infected wound. An ample amount of easily digested foods and sufficient fluids to insure 1 liter or more of urinary output are important. The Semi-Fowler position, and having the patient lie on her side and abdomen facilitate drainage. An ice-bag over the uterus has a stimulating and pain-relieving quality. Rest is essential, and is best secured by competent nursing and adequate use of morphine or codeine.

Ergot preparations should be used both because of their effect on uterine tone and their stimulating effect on the reticulo-endothelial system.^{48,49} Antipyretic drugs and cathartics are generally contraindicated. A low enema and forced fluids are recommended instead.

Connally¹⁴ has found that 5 mg. per day of stilbestrol, administered during the 1st few days of the puerperium, reduced the incidence of morbidity to less than one-third that of a control group of patients not receiving this drug. In patients where lactation is contraindicated or undesired, stilbestrol may be of benefit.

Blood transfusions are of utmost importance in the treatment of puerperal infection.⁶² Excessive blood loss during delivery should be replaced prophylactically. All blood should be properly typed and cross-matched. Rh positive blood must

not be given to an Rh negative patient. This is especially true where future pregnancies and repeated transfusions are to be considered. Small transfusions of 250 to 350 cc. may be given daily or less frequently as indicated by the course of the disease. They should be employed early, and before the onset of alarming symptoms and be continued until recovery is certain.

There is no universally recognized treatment of phlebitis, thrombophlebitis and phlebothrombosis during the puerperium. The prophylactic practices of wrapping the legs immediately after delivery of those patients having varicosities, and getting obese women out of bed early in the puerperium are well worth following. Elevation and wrapping of both legs, heat cradle, keeping the patient well hydrated and at rest are the usual conservative methods of therapy. Chemotherapy should be used in the presence of a temperature rise. Mengert's study⁵³ showing that the uncomplicated obstetric patient stands only 1 chance in almost 35,000 of embolic death from bland thrombosis, emphasizes the importance of guarding against interfering with Nature's efforts. The recent reports advising surgical treatment⁶⁸ and anticoagulant therapy¹⁶ must be critically interpreted. Obstetrical patients will probably experience far greater danger from the anesthetic and operation than they will from the disease. The complications of heparin and dicumarol therapy must be kept constantly in mind and the prothrombin level and coagulation time must be carefully followed. Therefore the postpartum patients eligible for these types of therapy must be carefully selected. The use of continuous caudal anesthesia in acute thrombophlebitis, to counteract the tendency of vasoconstriction, may prove itself a worthwhile addition to the management of the disease, but the dangers of this type of anesthesia must be recognized.

Surgical measures are limited to incision and drainage of pelvic abscesses. When a pelvic abscess points in the vaginal cul-

de-sac and is fluctuant, it should be drained by colpotomy. If the abscess points on the lateral anterior abdominal wall and fluctuation can be demonstrated, incision and drainage is indicated.

Recovery is the rule in puerperal infection. The majority of all cases which are included under morbidity rates are symptom-free and show only the changes of fever, leukocytosis and elevation of the pulse rate. Any therapeutic measure that interferes with Nature's efforts to limit and eradicate the infection is contraindicated.

CHEMOTHERAPEUTIC AND ANTIBIOTIC AGENTS. *Sulfonamides*. Parasulfonamide benzene-azo compounds and their derivatives were proved to have bactericidal qualities in 1919 by Heidelberger and Jacobs of the Rockefeller Institute. In 1935 Domagk¹⁸ in Germany showed that this azo-dye had a selective curative action in streptococcic infections of mice. Colebrook and Kenny¹³ in London (1936) showed excellent results with prontosil in the treatment of puerperal hemolytic streptococcic infection. Further chemical research resulted in the development of sulfanilamide and its derivatives. Their therapeutic value has been established in the treatment of infections caused by the hemolytic streptococcus, staphylococcus, pneumococcus, gonococcus, and *Clostridium welchii*. Their value seems to be questionable in the treatment of anaërobic streptococcal infections.

According to Gibberd,²⁴ the reduction in mortality of sulfonamide treated hemolytic streptococcus infections was associated mainly with a decrease in the widespread invasion of the tissues by the hemolytic streptococcus, rather than with a greater tendency to resolution of the disease, once widespread invasion had occurred. Foulis and Barr²² obtained a mortality rate of 1.4% in their series of patients with puerperal sepsis treated with the sulfonamides. This they compared with a mortality rate of 13.4% in the preceding 5 year period when no chemotherapy was used. Sulfonamides

were given prophylactically to 493 puerperal women by Delmas and deKerleau¹⁹ with a slight decrease in mortality and a considerable reduction in morbidity. Many other investigators^{28,44,55} have used the sulfonamides in puerperal infections.

The sulfonamides most widely used at the present time are sulfadiazine, sulfathiazole and sulfamerazine. The complications of the sulfonamides include agranulocytosis,²³ acute hemolytic anemia, toxic dermatoses, urinary complications, and others less frequently seen.^{47,61} Maintenance of the urinary output is the cardinal principle involved in prevention of urinary complications.

Penicillin. Penicillin is effective against the organisms usually found in cervical cultures, and should prove to be the drug *par excellence* in the prevention and treatment of puerperal infections.

In general, the gram-positive organisms are sensitive to penicillin, as also are the gram-negative cocci. The gram-negative bacilli are relatively insensitive. However, many of the gram-negative bacilli formerly considered totally insusceptible to penicillin are now known to be sensitive in various degrees, although far less so than the gram-positive bacilli.^{31,65,71} Infections due to gram-negative organisms of any kind should not necessarily be considered outside the scope of penicillin therapy. Case reports are now appearing in which penicillin therapy has been successful in curing infections due to organism hitherto classed as resistant to penicillin.^{33,40}

To date, most of the work concerning the use of penicillin in obstetrics has been to prove its transmission across the placenta to the fetal circulation and amniotic fluid.^{27,32,38,80} Its prophylactic use in patients with prolonged labor and in those with premature rupture of the membrane has been suggested.

Synergism of penicillin with sulfonamides has not been established. Kirby³⁹

regards the action as additive rather than synergistic. The War Department Technical *Bulletin*⁷² for March 1945 states that there is no clinical evidence of synergism between the 2 agents, and that the supplementary use of sulfonamides only contributes to the risk of untoward reactions and complications. Hobby and Dawson³⁵ have observed that sulfonamide *in vitro* increases the bacteriostatic action of penicillin only if the organism is sulfonamide-sensitive and present in small numbers. Douglas and Davis²⁰ believe that in mixed puerperal infections, where gram-positive cocci and gram-negative bacilli are present, both penicillin and sulfadiazine should be employed. Conclusions as to the benefit of combining the 2 drugs must await adequate chemical and clinical evidence.

The daily dose of penicillin varies with the type and severity of the infection. The tendency seems to be to use much larger doses of the drug if the usual daily doses of 100,000 to 200,000 units do not result in a clinical response. In severe infections the drug should be continued for several days after the temperature and pulse have become normal.

Streptomycin. Streptomycin, an antibiotic substance obtained from the mold *Actinomyces griseus*, supplements penicillin by arresting the growth of many of the gram-negative bacilli. It is freely distributed in the fetal circulation and amniotic fluid following intravenous administration to the mother at term.⁷⁹ At this time, insufficient clinical studies have been reported in its use in puerperal infections, but there is reason to believe it will prove itself a valuable addition to our present armamentarium.

Among the causes of maternal mortality, sepsis has dropped from first place, which it long held, to third.⁵⁷ This improvement is due to better obstetrical practice in general, and to the chemotherapeutic and antibiotic drugs.

REFERENCES

- (1.) Adair, F. L., and Hac, L. R.: New York State J. Med., 41, 2318, 1941. (2.) Aycock, W. L., and Foley, G. E.: Am. J. Med. Sci., 211, 350, 1946.

- (3.) Batisweiler, J.: *Arch. f. Gynäk.*, 157, 582, 1934. (4.) Beck, A. C.: *Obstetrical Practice*, Baltimore, Williams & Wilkins, p. 740, 1942. (5.) Bernstein, J. B., and Otten, R. E.: *Am. J. Obst. and Gynec.*, 31, 37, 1936. (6.) Brown, R.: *Med. Ann. Dist. of Columbia*, 12, 15, 1943. (7.) v. Buben, I.: *Zentralbl. f. Gynäk.*, 48, 1310, 1924. (8.) Bumm, E.: *Arch. f. Gynäk.*, 40, 398, 1891. (9.) Bumm, E.: *Beitr. z. Geburtsh. u. Gynäk.*, 8, 329, 1904.
- (10.) Colebrook, L., and Hare, R.: *J. Obst. and Gynec., Brit. Emp.*, 40, 609, 1933. (11.) Colebrook, L.: *Lancet*, 1, 1085, 1935. (12.) Colebrook, L.: *J. Obst. and Gynec., Brit. Emp.*, 43, 691, 1936. (13.) Colebrook, L., and Kenny, M.: *Lancet*, 1, 1279, 1936. (14.) Connally, H. F., Jr.: *Am. J. Obst. and Gynec.*, 46, 125, 1943. (15.) Conti, E. A., O'Loughlin, D. L., McMeans, J. W., and Lipman, G. S.: *Surg., Gynec. and Obst.*, 73, 367, 1941.
- (16.) Davis, A., and Porter, M.: *Brit. Med. J.*, 1, 718, 1944. (17.) DeLee, J. B.: *Principles and Practice of Obstetrics*, 7th ed., Philadelphia, Saunders, p. 932, 1940. (18.) DeLee, J. B., and Greenhill, J. P.: *Year Book of Obstetrics and Gynecology*, p. 265, 1937. (19.) Delmas, P., and de Kerleau, J. C.: *Bull. Soc. gynéc. et d'obst.*, 27, 711, 1938. (20.) Douglas, R. G., and Davis, I. F.: *Am. J. Obst. and Gynec.*, 51, 352, 1946.
- (21.) Eastman, N.: *Am. J. Obst. and Gynec.*, 47, 445, 1944. (22.) Foulis, M. A., and Barr, J. B.: *Brit. Med. J.*, 1, 445, 1937.
- (23.) Gayus, I. K., Green-Armytage, V. B., and Baker, J. K.: *Brit. Med. J.*, 2, 560, 1939. (24.) Gibberd, G. F.: *J. Am. Med. Assn.*, 109, 598, 1937. (25.) Goodall, J. R.: *Gynecology and Obstetrics*, C. H. I. Davis, Hagerstown, Md., W. F. Prior, 21, 1, 1939. (26.) Gordon, A.: *A Treatise in Epidemic Puerperal Fever*, London, 1795. (27.) Green, H. J., and Hobby, G. L.: *Proc. Soc. Exp. Biol. and Med.*, 57, 282, 1944.
- (28.) Hanley, B. J., and Golenternek, D.: *West. J. Surg.*, 47, 137, 1939. (29.) Harris, J. W., and Brown, J. H.: *Am. J. Obst. and Gynec.*, 2, 497, 1926. (30.) Harris, J. W., and Brown, J. H.: *Bull. Johns Hopkins Hosp.*, 44, 1, 1929. (31.) Helmholtz, H. F., and Qung, C.: *Am. J. Dis. Child.*, 68, 236, 1944. (32.) Herrell, W. E., Nichols, D. R., and Heilman, D. H.: *J. Am. Med. Assn.*, 125, 103, 1944. (33.) Hersh: *Arch. Otolaryngol.*, 41, 204, 1945. (34.) Hill, A. M.: *Med. J. Australia*, May 3, 1941. (35.) Hobby, G. L., and Dawson, M. H.: *J. Bact.*, 49, 416, 1945. (36.) Holmes, O. W.: *New England Quart. Med. and Surg.*, April 1843. (37.) Horn, L. L.: *Monatschr. f. Geburtsh. u. Gynäk.*, 95, 43, 1933. (38.) Hunter, A. M., and Parks, J.: *Am. J. Obst. and Gynec.*, 49, 663, 1945.
- (39.) Kirby, W. M. M.: *Proc. Soc. Exp. Biol. and Med.*, 57, 149, 1944. (40.) Kobacher, J. L., and Mehlin, G. B.: *Am. J. Med. Sci.*, 210, 66, 1945. (41.) Kochmann, G.: *Monatschr. f. Geburtsh. u. Gynäk.*, 93, 154, 1933. (42.) Koller, T.: *Schweiz. med. Wchnschr.*, 64, 389, 1934. (43.) Kulka, E.: *Arch. f. Gynäk.*, 152, 152, 1932.
- (44.) Laurbillon, J., and LeJeune, A.: *Bruxelles méd.*, 19, 252, 1938. (45.) Liubimowa, M. P.: *Zentralbl. f. Gynäk.*, 50, 1466, 1926. (46.) Logan, J.: *J. Obst. and Gynec., Brit. Emp.*, 38, 788, 1931. (47.) London Letter, *J. Am. Med. Assn.*, 109, 515, 1937. (48.) Louros, N., and Scheyer, H. E.: *Zentralbl. f. Gynäk.*, 51, 763, 1927. (49.) Louros, N.: *Klin. med. Wchnschr.*, 7, 996, 1928.
- (50.) Mayes, H. W.: *West. J. Surg.*, 51, 201, 1943. (51.) Meleney, F. L.: *Am. J. Obst. and Gynec.*, 16, 180, 1928. (52.) Mengert, W. F.: *Journal-Lancet*, 58, 517, 1928. (53.) Mengert, W. F.: *Am. J. Obst. and Gynec.*, 50, 338, 1945. (54.) Morosova and Associates: *Arch. f. Gynäk.*, 159, 1551, 1935. (55.) Morris, T. J.: *Am. J. Obst. and Gynec.*, 38, 67, 1939. (56.) Mudalian, A. L., and Memon, C. K.: *Zentralbl. f. Gynäk.*, 57, 674, 1933.
- (57.) Newberger, C.: *Illinois Med. J.*, 87, 136, 1945. (58.) Paine, C. G.: *Brit. Med. J.*, 1, 243, 1935. (59.) Pasteur, L.: *Bull. de l'Acad. de méd., Paris*, 8, 256, 1879. (60.) Pastore, J. B.: *Am. J. Obst. and Gynec.*, 31, 78, 1936. (61.) Paton, J. P., and Eatou, J. C.: *Lancet*, 1, 1159, 1937. (62.) Polak, J. O.: *Am. J. Obst. and Gynec.*, 10, 521, 1925.
- (63.) Rothhaus, E.: *Arch. f. Gynäk.*, 130, 727, 1927. (64.) Schwarz, O. H., and Dieckmann, W. J.: *Am. J. Obst. and Gynec.*, 13, 467, 1927. (65.) Schwartzman, G.: *Science*, 100, 477, 1944. (66.) Semmelweis, I. P.: *Aetiologie, Begriff und Prophylaxis des Kindbettfiebers*, Leipzig, 1861. (67.) Smith, Jr.: *J. Obst. and Gynec., Brit. Emp.*, 40, 991, 1933. (68.) Smith, H. G.: *J. South Carolina Med. Assn.*, 41, 85, 1945. (69.) Steinhorn, S. R.: *Am. J. Obst. and Gynec.*, 50, 63, 1945. (70.) Stout, M. L.: *Am. J. Obst. and Gynec.*, 29, 588, 1935.
- (71.) Thomas, A., Jr., and Levine, M.: *J. Bact.*, 49, 623, 1945. (72.) War Dept. Tech. Bull., *War Med.*, 7, 234, 1945. (73.) Watson, B. P.: *J. Am. Med. Assn.*, 103, 1745, 1934. (74.) Watson, B. P.: *Canad. Med. Assn. J.*, 38, 135, 1938. (75.) Weigert, C.: *Ueben Pockenähnliche Gebilde in parenchymatösen Organen und deren Beziehung Bacteriencolonien*, Breslau, 1875. (76.) White, C.: *Treatise on the Management of Pregnant and Lying-in Women*, London, 1773. (77.) Williams, J. T.: *J. Am. Med. Assn.*, 99, 1, 991, 1932. (78.) Williams, N.: *Obstetrics*, 6th ed., New York and London, Appleton, 1930. (79.) Woltz, J. H. E., and Wiley, M.: *Proc. Soc. Exp. Biol. and Med.*, 60, 106, 1945. (80.) Woltz, J. H. E., and Zintel, H. A.: *Am. J. Obst. and Gynec.*, 50, 338, 1945.
- (81.) Ziegler, C. E., and Austin, B. R.: *Penna. Med. J.*, 43, 1452, 1940.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 16, 1946

Studies on Nutrition. The Effect of Preoperative Force Feeding on Surgical Patients. C. E. KOOP, M.D., J. DREW, M.D., C. RIEGEL, Ph.D., and J. E. RHOADS, M.D. (Dept. of Surgery and Harrison Dept. of Surg. Research, Univ. of Penna.). A group of 24 patients undergoing major abdominal or intracranial operations have been studied for the effect of preoperative force feeding on the postoperative course. Of these patients, 12 were "force fed" approximately 0.9 gm. of nitrogen per kg. per day (about 3 times the average postoperative requirement) for 5 preoperative days. The remaining 12 patients served as controls.

Among the nutritional studies carried out before and after operation were nitrogen balance determinations, serum protein concentrations, and total circulating proteins.

Circulatory studies included blood and plasma volume determinations, the response of the patient's pulse, blood pressure and the state of consciousness to changes in position from the horizontal to the vertical on a tilt table, and ballistocardiographic tracings. These determinations were made at intervals before and after operation.

It was found that patients undergoing gastrectomy, colon resection and craniotomy could accumulate a nitrogen store well in excess of the deficit usually observed on inadequate intake after operation if they were force fed for 5 days preoperatively. This accumulation varied from 81 to 257 gm. of nitrogen for the 5 days.

Objective evidence obtained with the ballistocardiograph and the tilt table supported the clinical impression that the postoperative course is improved provid-

ing there is a sufficient preoperative accumulation of nitrogen to compensate for the deficit in the immediate postoperative period.

Relation of Nitrogen Balance and Blood Volume to Abnormalities of the Circulation in Convalescent Surgical Patients. R. L. MAYOCK, M.D., C. E. KOOP, M.D., C. RIEGEL, Ph.D., N. T. KOUGH and ISAAC STARR, M.D. (Dept. of Therap. Research and the Harrison Dept. of Surg. Research, Hosp. of the Univ. of Penna.). The ballistocardiogram has been used in a search for abnormalities of convalescence following surgical operations. On 67 patients, 362 ballistocardiograms were made; in many of them nitrogen balance studies had been made. Abnormal ballistocardiograms were found more frequently in the patients whose nitrogen balance after operation became negative than in those whose balance was maintained by special feeding methods. This difference was statistically significant.

Cardiac output as calculated from the ballistocardiogram was compared with the result of estimations of blood volume made by the blue dye T-1824. There was significant positive correlation between cardiac output and blood volume, but the relationship was not a close one and changes in single individuals were sometimes the reverse of this relationship.

These results and other clinical criteria support the conclusion that the patients kept in nitrogen equilibrium by special feeding methods were actually in better physical condition than those allowed to go into negative nitrogen balance.

Electroencephalographic Evaluation of the Effect of Penicillin in Treatment of Central Nervous System Syphilis.* DONALD SCOTT, JR., PH.D., and GEORGE D. GAMMON, M.D. (Johnson Foundation for Med. Physics and Dept. of Neurology, Univ. of Penna.). Previous workers have reported the presence of significant abnormalities in the electroencephalographic record from cases of central nervous system syphilis. The present study of 30 cases found abnormal records in 60%, but the main interest was in developing the electroencephalogram as a method of evaluating the effect of penicillin treatment.

The patients were divided into 4 groups on a clinical basis (juvenile paresis, 3 cases; meningovascular syphilis, 8 cases; taboparesis, 9 cases; paresis, 10 cases). The electroencephalographic records were classed as either normal, questionable, or abnormal. The greatest percentage of abnormal records was seen among the paretic cases (70%), whereas the lowest incidence was seen in taboparesis (11%). In all cases where the pretreatment record was taken to be abnormal, a reduction in this type of activity was found when the patient was restudied after treatment. It was more difficult, however, to determine such changes in records which were originally considered questionable and no clear-cut shift could be seen in this group after treatment. In general, there was a rough correlation between the reduction in abnormality in the electroencephalogram and the clinical improvement in the patient. However, in most cases there was a residuum of minor abnormality after treatment, which agreed with the fact that in most cases the patient had not entirely recovered at the time the last electroencephalogram was made.

* This work was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Pennsylvania. The University of Pennsylvania penicillin group includes Dr. John H. Stokes, responsible investigator, and Drs. Beerman, Ingram, Steiger, Gyorgy, Rose and Steele.

Of great interest was the prominence of the moderately slow (5 to 8 per second) waves in pretreatment records. These were present in 72% of the abnormal and questionable records. It was also found that in 56% of these records the alpha rhythm had a frequency below normal limits. It was hard to distinguish between these 2 situations, but where the frequency returned to the normal alpha range after treatment it was considered that the moderately slow waves were essentially an alpha pattern which had been slowed by the disease process. Whatever the correct identification of this activity the most noticeable change during treatment was the gradual disappearance or speeding up of the waves with frequencies between 5 to 8 per second.

Effect of Globin From Human Erythrocytes on Plasma Volume and Diuresis.*

MAX M. STRUMIA, M.D. (Bryn Mawr Hosp. and Graduate School of Medicine, Univ. of Penna.). The administration of a 4% solution of modified human globin made isotonic with sodium chloride or dextrose produces a rapid increase in blood volume closely equivalent to the amount given, as determined by plasma volume studies with the dye method. This increased plasma volume in the normal subject usually disappears at the end of 24 hours. Less than 5% of globin is lost in the urine and the bulk of the material appears to be utilized.

In the management of the nephrotic state of chronic and subacute glomerulonephritis, edema offers a challenge to the attending physician. A salt-poor diet, moderate and carefully controlled water reduction, a protein intake sufficient not only to maintain a positive balance but also to restore progressively lost protein reserve, proper cardiac stimulation if signs

* This work has been initiated with the aid of the Plasma Research Fund of the Bryn Mawr Hospital, and continued under contract recommended by the Committee on Medical Research of the Office of Scientific Research and Development.

of insufficiency exist, these are the basic elements of therapy. They are not, however always sufficient.

It is often necessary to reduce or eliminate edema by means of diuretics. As diuretic agents, urea, potassium chloride, ammonium chloride, mercopurin, plasma, human serum albumin, globin have been used with varying degrees of success.

In a series of carefully controlled experiments, globin has produced in patients suffering from chronic glomerulonephritis in the nephrotic state a prompt and abundant diuresis, with rapid disappearance of visible edema. During the period

of observation, no restrictions were placed on the salt and water intake. Globin has proven effective as a diuretic whether the patient was in a positive nitrogen balance or not. Similar results have been obtained on hypoproteinemic edemas. In the cases so far studied, globin was employed as a 4% solution in 0.85% sodium chloride. Even better effect can be expected when globin is made isotonic with dextrose. Kidney functional studies done before and after administration of large doses of globin to nephrotic patients have shown no change. Two cases were presented in detail.

BOOK REVIEWS AND NOTICES

VITAMINS AND HORMONES. Advances in Research and Applications. Vol. III. Edited by ROBERT S. HARRIS and KENNETH V. THIAMIN. Pp. 452. New York: Academic Press, Inc. Price, \$6.50.

THE 3rd volume of "Vitamins and Hormones" covers 9 subjects as follows: The Interrelation of Vitamins, by Thomas Moore; The Synthesis of B Vitamins by Intestinal Bacteria, by Victor A. Najjar and Rachel Barrett; Sulfonamides and Vitamin Deficiencies, by Floyd S. Daft and W. H. Sebrell; Manifestations of Prenatal Nutritional Deficiency, by Josef Warkany; Growth Factors in Microbiology—Some Wider Aspects of Nutritional Studies With Microorganisms, by B. C. J. G. Knight; Possibilities in the Realm of Synthetic Estrogens, by E. C. Dodds; Chemistry of Anti-pernicious Anemia Substances of Liver, by Y. Subbarow, A. Baird Hastings, and Milton Elkin; The Mechanism of Action and Metabolism of Gonadotropic Hormones in the Organism, by Bernhard Zondek and Felix Sulman; The Role of Acetylcholine in the Metabolism of Nerve Activity, by David Nachmansohn.

This volume follows the same general plan of the first two and on the whole the articles are as well written; however, a few comments may be in order. There is some repetition in the second and third articles that probably could have been eliminated. In the article on prenatal nutritional deficiency, one is surprised to find so little regarding the effect of vitamin E. The review on growth factors in microbiology is more a monograph in itself than a chapter of a book. It takes up over 100 pages and covers the literature of this rapidly developing field in a masterly fashion.

The article on synthetic estrogens is largely a review of the author's own work and suggestions for future work. The author of the last article presents a good case for the acetylcholine theory of nerve conductance.

The difficulty of preparing such a volume and getting it into the hands of the reader in a fairly short time is emphasized by the

fact that mention of pyridoxal, pyridoxamine, desthiobiotin, etc., and their activities in bacterial metabolism, was made only in notes added in proof. There are a few typographical errors such as on page 241 where Fitz-Hugh has become Fritz Hugh.

J. J.

PRINCIPLES OF DYNAMIC PSYCHIATRY. By JULES H. MASSERMAN, M.D., Division of Psychiatry, Dept. of Medicine, Univ. of Chicago. Pp. 322; 4 plates. Philadelphia: Saunders, 1946. Price, \$4.00.

THE expressed purpose is to record here certain fundamentals of modern dynamic psychiatry, as yet only taught through lecture and precept. Another volume is to follow, entitled "Practice of Dynamic Psychiatry." In this book, Part I gives the scope of psychiatry, together with a critical consideration of behavioristic theories. Part II attempts to "reformulate and integrate these theories into a biodynamic organon of behavior."

Among the many topics discussed are: Psychiatry, the Science of Behavior; Psychologic Concepts of Behavior; Psychoanalytic Concepts of Behavior; The Dynamics of Adaptation; Neurotogenic Dynamisms; Psychotic Dynamisms; Biodynamic Correlates of Current Theories of Behavior; Development of a General Biodynamic Theory of Behavior; Biodynamic Formulations of Behavior; The Principle of Substitution; Principle of Conflict; Intensity of Conflict and Modes of Therapy; Biodynamic Processes of Language and of "Verbal" Therapy; A Critique of the Biodynamic Theory of Behavior. Most space is accorded Schizophrenic Mechanisms, discussed as Withdrawal from "External Contacts," and Blunting and Distortion of Affect, Thinking Disturbances in Schizophrenia, and Disturbances in Motor Patterns.

Throughout, the approach is definitely psychoanalytic, with the usual colorful wording, thereby rendering its exceptionally informative Glossary desirable. N. Y.

CLINICAL ROENTGENOLOGY OF THE HEART.
 Edited by JOHN B. SCHWEDEL, M.D.
 Pp. 380; 749 illus. New York, Hoeber,
 1946. Price, \$12.00.

THIS book is unquestionably one of the easiest to read concerning roentgenology of the heart that has yet been published. While this is partially due to the author's literary style, of more importance is the manner in which he has organized his material.

The book is divided into 14 chapters: The first 2 deal with technique and cardiac measurements; Chapters 3 and 4 concern the normal heart and its normal variations; Chapters 5, 6, 7 and 8 are particularly noteworthy as each chapter is devoted to one chamber of the heart. These should prove of considerable assistance to the student and certainly helps crystallize the thoughts of the trained radiologist. The author treats the aorta, venæ cavæ and the brachiocephalic vessels in the same way. The chapter on "Lungs and Heart Disease" deserves special comment. Its illustrations and microphotographs of lung sections are particularly instructive.

The pericardium, congenital heart disease, displacements of the heart, and cardiac and extracardiac calcifications are also treated in individual comprehensive chapters.

The publishers have done an excellent job. The paper used is of fine quality and the printing is large enough to read with ease.

Each roentgenogram is accompanied by an explanatory line-drawing; these are particularly valuable as they clearly illustrate the significant anatomic findings. The legends are uniformly clear and add considerably to the text. Unfortunately, the film reproductions are all positive prints, but their excellence compensates in large measure for this deficiency.

P. H.

ADVANCES IN CARBOHYDRATE CHEMISTRY.
 Vol. I. By W. W. PIGMAN, B.S., A.M.,
 PH.D., Corn Products Refining Co., Argo,
 Ill.; and M. L. WOLFROM, A.B., M.S.,
 PH.D., Ohio State Univ., Columbus, O.
 Pp. 374. New York: Academy Press,
 1945. Price, \$6.00.

THIS book represents the first of a projected series of annual volumes to review important advances in the chemistry of carbohydrates including the sugars, poly-

saccharides and glycosides. Thirteen contributors join in the presentation of the 11 following reviews: The Fischer Cyanhydrin Synthesis and the Configurations of Higher-carbon Sugars and Alcohols (C. S. Hudson), 36 pages; The Altrose Group of Substances (N. K. Richtmyer), 40 pages; Carbohydrate Orthoesters (Eugene Pacsu), 51 pages; Thio- and Seleno-Sugars (A. L. Raymond), 17 pages; The Carbohydrate Components of the Cardiac Glycosides (R. C. Elderfield), 27 pages; Metabolism of the Sugar Alcohols and Their Derivatives (C. J. Carr and J. C. Krantz, Jr.), 18 pages; The Chemistry of the Nucleic Acids (R. S. Tipson), 53 pages; The Fractionation of Starch (T. J. Schoch), 32 pages; Preparation and Properties of Starch Esters (R. L. Whistler), 31 pages; Cellulose Esters of Organic Acids (C. R. Fordyce), 19 pages; A Discussion of Methods of Value in Research on Plant Polyuronides (Ernest Anderson and Lila Sands), 16 pages.

The authors have presented critical reviews of their respective subjects. Most of the reviews are of analytical and industrial interest though the contribution by Elderfield, Carr and Krantz, and Tipson are of definite biochemical interest. Adequate literature references are presented.

H. V.

HIDDEN HUNGER. By ICIE G. MACY, PH.D.,
 Research Laboratory, Children's Fund of
 Michigan; and HAROLD H. WILLIAMS,
 B.S., PH.D., Research Laboratory, Chil-
 dren's Fund of Michigan. Pp. 286. Lan-
 caster, Pa.: Cattel Press, 1945. Price,
 \$3.00.

"HIDDEN HUNGER, Tragedy of the Unbalanced Diet" is a skillfully written record of the achievements and failures in applied nutrition. It provides an up-to-date and scientifically accurate story of the development of the field of nutrition. It places a major emphasis upon the improvement of human welfare through better nourishment, and in this respect is a natural outgrowth of the senior author's active rôle in research and in national conferences on health and nutrition.

A strong indictment is leveled against the nation for its failure to apply the recommendations of the White House Conference on Child Health and Protection (1930). If they had been adopted, perhaps the large

rejection rate of Selective Service candidates upon physical grounds would have been much reduced.

The nutrition of the infant, the child, the adult and the aged is discussed. Interesting comparisons are made of the Army rations and feeding practices in World Wars I and II. Much instructive information is given upon the experiences in improving the meals of factory workers during the war.

Relevant data and quotations are presented from many reports that are not readily available to the lay reader. There is an extensive bibliography, which is well indexed. It should appeal to readers in many fields of endeavor.

H. V.

ADVANCES IN PROTEIN CHEMISTRY. Vol. II.

By M. L. ANSON, Continental Foods, Hoboken, N. J.; and JOHN T. EDSALL, A.B., M.D., Harvard Med. School, Boston, Mass. Pp. 443. New York: Academic Press, 1945. Price, \$6.50.

THIS is the second annual volume of a series concerned with recent advances in protein chemistry. Eleven chapters are devoted to reviews in the following fields: Analytical Chemistry of the Proteins (A. J. P. Martin and R. L. M. Synge), 63 pages; The Microbiological Assay of Amino Acids (E. E. Snell), 31 pages; The Amino Acid Composition of Food Proteins (R. J. Block), 13 pages; The Relationship of Protein Metabolism to Antibody Production and Resistance to Infection (P. R. Cannon), 18 pages; Terminal Amino Acids in Peptides and Proteins (S. W. Fox), 21 pages; The Copper Proteins (C. R. Dawson and M. F. Mallette), 62 pages; Mucoids and Glycoproteins (Karl Meyer), 23 pages; The Reactions of Formaldehyde with Amino Acids and Proteins (Dexter French and J. T. Edsall), 56 pages; Wheat Gluten (M. J. Blish), 21 pages; Protein Denaturation and the Properties of Protein Groups (M. L. Anson), 24 pages; X-Ray Diffraction and Protein Structure (I. Fankuchen), 17 pages.

Martin and Synge give the most extensive review of analytical methods available, documenting their discussion with well over 800 references. The review of microbiologic assay methods by Snell summarizes the available data in this rapidly developing field. Meyer's review of mucoids and glyco-

proteins is the first to appear in this field since Levene's monograph in 1925.

Many factual data appear as tables or charts in each chapter. Bibliographies are extensive and up-to-date. Few errors in proofreading are apparent. This volume can be recommended highly to all interested in proteins and amino acids.

H. V.

THE FALLING SICKNESS. By OWSEI TEMKIN, M.D. Pp. 380. Baltimore: Johns Hopkins Press, 1945. Price, \$4.00.

THE nature of epilepsy being still obscure and the border-line between the epilepsies and other nervous diseases indistinct, the author recognizes that its history cannot be written in the same sense that one might construct a history of tuberculosis, for instance. He has, therefore, called his book by the ancient name "The Falling Sickness," and has aimed at finding out what he could about "what was meant by epilepsy, what symptoms were attributed to it, how it was explained, and how treated" through its long past. Beginning with the ancient Greeks, the author has chosen to close with the period about 1880, "when the impact of Jackson's and Charcot's work made itself felt." This last item has required some 30 odd pages that are more in the domain of the neurologist than of the historian; however, it is handled with such a sure touch that one regrets that the same skill was not applied to the rich history of epilepsy in the past 60 years as well. To be sure, the more recent the events, and the greater their number, the more difficult is the historian's task; but we can be confident that the result would have been far more than a mere catalogue of names and—just as in the case of the Charcot-Jackson discussion—would have helped further to understand the present status of the subject. When the author has so well completed his self-appointed task, one should not, perhaps, cry for more. Yet one cannot help but wish that the story had been made more complete by the inclusion also of a consideration of epilepsy among the primitives and in Far Eastern civilizations. We know of no full history of the subject in English in spite of all that has been written about it.

An adequate detailed critical review of this scholarly monograph could scarce be done except by another professional histor-

ian of medicine. Nor could such a review be reproduced in, or suitable for, a journal such as this one. However, we can guarantee that a careful perusal of this excellent study will provide the reader with much more medical history than that included in the history "The Falling Sickness."

E. K.

EXERCISES IN HUMAN PHYSIOLOGY. By SIR THOMAS LEWIS, University College, London. Pp. 103; 8 illus. London: MacMillan, 1945. Price, \$1.25.

THIS small book lives up to the reputation of its author. It describes a number of relatively simple fundamental experiments that Sir Thomas himself developed. He has selected those most readily applicable to the teaching of medical students, omitting the more elaborate and painful experiments for which he is so justly renowned. Many of the experiments described are commonly utilized for teaching, such as venous pressure estimates (direct and indirect methods), indirect arterial pressure measurements, arterial and venous pulse curves, electrocardiograms, and histamine reactions. Others less commonly considered are local anesthetization of the ulnar nerve, vasomotor reactions to temperature, reactive hyperemia, inflammatory hyperesthesia, etc. All the experiments described are useful and the book should be of great value to teachers. Even in the familiar experiments, the descriptions are given a new value by the inclusion of Sir Thomas' own clinical viewpoint and by his insistence on the necessity of careful observation.

The only criticism that might be raised is that the exercises are for the most part qualitative. The newer elaborate mechanical devices that make qualitative studies now more accurate and complete are not considered. For this reason the work is perhaps the better for the training of medical practitioners and the worse for the development of physiologists and clinical research workers.

H. B.

BIOLOGICAL ACTIONS OF SEX HORMONES. By HAROLD BURROWS. Pp. 514. Cambridge University Press, 1945. Price, \$8.50.

THE purpose of this book is to coördinate and summarize experimental findings in the

field of the sex hormones. It is confined largely to biologic work done in the laboratory rather than the clinic.

The Reviewer, who has put this book to the test of determining how usable it is, has found that, in the search for the experimental evidence that has established various facts, data could be readily found in considerable detail which otherwise would have necessitated laborious search through the literature. This means that the index is sufficiently detailed in cross-references and that the discussion of the literature has been well organized in the substance of the book. It can be highly recommended as a work for reference.

I. Z.

NEW BOOKS

Current Therapies of Personality Disorders. By BERNARD GLUECK, M.D., President, The American Psychopathological Association. Pp. 296. New York, Grune & Stratton, 1946. Price, \$3.50.

Treatment by Ion Transfer (Iontophoresis). By D. ABRAMOWITSCH, M.D., Physician-in-Charge of the Physiotherapy Dept., Lincoln Hosp., New York City; and B. NEOUSSIKINE, M.D., Tel-Aviv. Pp. 192; Bibliography and Index. New York: Grune & Stratton, 1946. Price, \$4.50.

Cosmetics and Dermatitis. By LOUIS SCHWARTZ, M.D., Medical Director, U. S. P. H. S.; Chief, Dermatoses Sect., Div. of Industrial Hygiene; Adj. Professor in Dermatology, Georgetown Univ. School of Medicine; Assoc. Clin. Professor in Dermatology and Syphilology, New York Univ. Coll. of Medicine; Consultant, Office of Price Administration; and SAMUEL M. PECK, M.D., Medical Director (R), U. S. P. H. S.; Assoc. Attend. Dermatologist, Mt. Sinai Hosp., New York City; Attend. Dermatologist and Syphilologist, Skin and Cancer Unit of the New York Post-Graduate Medical School and Hosp. of Columbia Univ.; Diplomate of the American Board of Dermatology and Syphilology. Pp. 198; 20 illus. New York: Hoeber, 1946. Price, \$4.00.

Doctors East, Doctors West. By EDWARD H. HUME, M.D. Pp. 278; 21 illus. New York: Horton, 1946. No price given.

An American physician's life in China.

Diseases of the Adrenals. By LOUIS J. SOFFER, M.D., Adj. Attend. Physician, The Mount Sinai Hosp., New York City. Pp. 304; 44 illus. Philadelphia, Lea & Febiger, 1946. Price, \$5.50.

The Herbal of Rufinus. By LYNN THORNDIKE (Editor, from the Unique Manuscript). With the assistance of FRANCIS S. BENJAMIN, JR. Pp. 467. Chicago: Univ. of Chicago Press, 1945. Price, \$5.00.

Corky the Killer. A Story of Syphilis. By HARRY A. WILMER, B.S., M.S., M.B., M.D., Ph.D. in Pathology. With an Introduction by PAUL A. O'LEARY, M.D., Head, Section on Dermatology and Syphilology, Mayo Clinic; Professor of Dermatology and Syphilology, Mayo Foundation, Univ. of Minnesota. Pp. 67; 33 illus. New York: American Social Hygiene Assn., 1946. Price, \$1.00.

This book is prepared for the lay public. It has a triple form of presentation, and is a combination of phantasy and fact to help remove public fears and misunderstandings relating to syphilis.

The Traumatic Deformities and Disabilities of the Upper Extremity. By ARTHUR STEINDLER, M.D., F.A.C.S., Professor and Head of the Dept. of Orthopedic Surgery, The State Univ. of Iowa; in collaboration with JOHN LOUIS MARXER, M.D., Assoc. Orthopedic Dept., the State Univ. of Iowa. Pp. 515; 1048 illus. Springfield, Ill.: Thomas, 1946. Price, \$10.00.

Physiotherapy. By THOMAS F. HENNESSEY, M.D., Dean and Director, Massachusetts School of Physiotherapy, Boston. Pp. 20. Indiana: Bellman, 1946. Price, \$.75.

The Venous Pulse and Its Graphic Recording. By FRANZ M. GROEDEL, M.D., Attend. Cardiologist, Beth David Hosp.; Cardiologist, St. Anthony's Hosp., New York City; Consult. Cardiologist, Einhorn Dept. of Lenox Hill Hosp., New York City. Pp. 223; 114 illus. Brooklyn, N. Y.: Medical Press, 1946. Price, \$5.50.

La Electroforesis de Sulfonamidas para el Tratamiento de los Procesos Infecciosoinflamatorios Localizados. By CAMILO SCHMEHLIK, DR. MED., Univ. de la Universidad de Viena f Licenciado de la Universidad de Madrid. Pp. 92. Madrid, Spain: Editorial Gran Capitan, 1945. No price given.

In this booklet the original text is given in Spanish, English, German and French

Unhappy Marriage and Divorce. By EDMUND BERGLER, M.D. With an Introduction by A. A. BRILL, M.D. Pp. 167. New York: International Univ. Press, 1946. Price, \$2.50.

A study of neurotic choice in marriage partners.

Motor Disorders in Nervous Diseases. By ERNST HERZ, M.D., Instructor in Neurology, Coll. of Physicians and Surgeons, Columbia Univ.; and TRACY J. PUTNAM, M.D., Professor of Neurology and Neurologic Surgery, Coll. of Physicians and Surgeons, Columbia Univ. Pp. 184; 250 illus. New York: King's Crown Press, 1946. Price, \$3.00.

The Medical Clinics of North America. Post-war Medicine. Pp. 485; 76 illus. Philadelphia: Saunders, 1946. Price, \$16.00 yearly.

Tratado de Cardioangiologia. By PEDRO A. TAPELLA, Docente Libre de Patologia Medica en la Facultad de Buenos Aires. Pp. 946. Buenos Aires: Lopez & Etchegoyen S.R.L., 1946. No price given.

Tratado de Patologia Medica por el DR. RODOLFO DASSEN, Laureado por la FAC. de Medicina de BS. AS (Medalla de Oro), Ex Docente Libre de Clinica Medica (BS. AS.), Medico del Hospital de Clinicas, Sala IV (BS. AS.). Pp. 827. Buenos Aires: Lopez & Etchegoyen S.R.L., 1946. No price given.

In English this "Medical Pathology" would probably be called a Text Book of Medicine, as it includes, in each of the diseases considered, a clinical description, diagnosis, prognosis and treatment as well as the different aspects of Pathology. Volume I covers Infectious Diseases, Diseases of the Cardiovascular System, the Blood and the Urinary Tract, also of the Spleen and Lymph Nodes. It contains a brief Index but no references.

Valor Pronostico del Electrocardiograma por el DR. MANUEL VELA. III. Ponencia. Pp. 336. Madrid: Libreria Editorial Cientifico Medica Espanola, 1946. No price given.

Publicaciones del Centro de Investigaciones Tisologicas. By ROQUE A. IZZO, Profesor. Pp. 280. Buenos Aires, Pabellon "Les Provincias," 1945. No price given.

Spezielle chirurgische Therapie für Studierende und Ärzte. Vol. 2. By DR. MAX SAEGESSER, Privatdozent für Chirurgie, Bern. Pp. 884. Bern: Medizinischer Verlag Hans Huber, 1946. Price, \$20.00.

Valor Pronostico del Electrocardiograma Apendice de Quadros Estadisticos por el DR. MANUEL VELA. III. Ponencia. Pp. 336. Madrid: Libreria Editorial Cientifico Medica Espanola, 1946. No price given.

It's How You Take It. By G. COLKET CANER, M.D., Associate in Neurology, Massachusetts General Hosp.; Psychiatrist in Dept. of Hygiene, Harvard Univ. Pp. 152. New York: Coward-McCann, 1946. Price, \$2.00.

The purpose of this book is to bring together common sense and useful information which every person over 16 should have about the use of the mind and effect of emotion, and about types of reactions to the opportunities and difficulties that everyone meets.

Journal of Colloid Science. Vol. I, No. 1 (bi-monthly). Editor-in-Chief, VICTOR K. LAMER, Columbia Univ., New York. New York: Academic Press, 1946. Price, \$10.00 yearly.

We welcome this new Journal in a special field closely allied to medicine and are confident that it will produce much valuable information and stimulation on matters that are of basic importance to all branches of biology. The high standing of its editors and consulting committee is a good guarantee that the undertaking will be well carried out.—E. K.

Asma Alergia por el DR. GUIDO RUIZ MORENO, Jefe de la Seccion Alergia del Instituto de Investigaciones Fisicas aplicados a la Patologia Humana, de la Academia Nacional de Medicine; Jefe del Consulerio de Algeria del Hospital Britanico de Buenos Aires; Miembro Titular de la Sociedad Argentina de Alergia; Membro Honorario del "American College of Allergists;" Miembro correspondiente de la "American Association for the Study of Allergy;" Miembro de "The International Correspondence Club of Allergy;" Docente Libre de Higiene y Medicina Social de la Facultad de Ciencias de Buenos Aires. Pp. 186. Buenos Aires: Lopez & Etchegoyen S.R.L., 1946. No price given.

Digitalis and Other Cardiotonic Drugs. By ELI ROBIN MOVITT, M.D., Capt., M.C., A.U.S.; Diplomate of American Board of Internal Medicine; Internist, Veterans Administration Facility, San Francisco, Calif. Pp. 203. New York: Oxford Univ. Press, 1946.

Enfermedades de los Pies. Vol. 40. Coleccion Espanola de Monografias Medicas, Director: DR. J. PUIG SUREDA. Pp. 128. No price given.

Essentials of Clinical Proctology. By MANUEL G. SPIESMAN, B.S., M.D., Proctologist, Mt. Sinai and Edgewater Hosps.; Consult. Proctologist, Grant, Henrotin and St. Elizabeth Hosps.; former Head of the Cook County Hosp. Rectal Clinic. With a Foreword by ANTHONY BASSLER, M.D., F.A.C.P., LL.D., Consult. Gastro-enterologist, St. Vincent's and other hospitals in New York City. Pp. 250; 62 illus. New York: Grune & Stratton, 1946. Price, \$4.00.

Shock Treatments and Other Somatic Procedures in Psychiatry. By LOTHAR B. KALINOWSKY, M.D., Res. Associate in Psychiatry, Coll. of Physicians and Surgeons, Columbia Univ., and New York State Psychiatric Inst. and Hosp.; Assist. Neurologist, Neurological Inst. of New York; and PAUL H. HOCH, M.D., Assist. Clinical Psychiatrist, New York State Psychiatric Inst. and Hosp.; Instructor in Psychiatry, Coll. of Physicians and Surgeons, Columbia Univ. With a Foreword by NOLAN D. C. LEWIS, M.D., Professor of Psychiatry, Coll. Physicians and Surgeons, Columbia Univ.; Director of the New York State Psychiatric Inst. and Hosp. Pp. 320. New York: Grune & Stratton, 1946. Price, \$4.50.

Scientific, Medical, and Technical Books Published in the United States of America, 1930-1944. Edited by R. R. HAWKINS, Chief of the Science and Technology Division, New York Public Library. Pp. 1114. New York: United States International Book Association, 1946. No price given.

NEW EDITIONS

Clinical Laboratory Diagnosis. By SAMUEL A. LEVINSON, M.S., M.D., PH.D., Director of Laboratories, Research and Educational Hosps., Chicago, Ill.; Professor of Pathology, Univ. of Illinois Coll. of Medicine; and ROBERT P. MACFATE, CH.E., M.S., PH.D., Assist. Director of Laboratories, Research and Educational Hosps., Chicago, Ill.; Asst. Professor of Pathology, Univ. of Illinois Coll. of Medicine. 3rd ed. Pp. 971; 207 illus. Philadelphia: Lea & Febiger, 1946. Price, \$10.00.

An Outline of Organic Nitrogen Compounds.
By EDWARD F. DEGERING, Dept. of Chemistry, Purdue Univ., and Collaborators. 4th ed. Pp. 752. Ypsilanti: Univ. Lithoprinters, 1945. Price, \$7.50.

Rehabilitation, Its Principles and Practice.
By JOHN EISELE DAVIS, M.D., Sc.D., Veterans Administration Facility, Perry Point, Md. 2nd ed. Pp. 264. New York: Barnes, 1946. Price, \$3.00.

Starling's Principles of Human Physiology.
By C. LOVATT EVANS, D.Sc., F.R.C.P., F.R.S., LL.D. (BIRM.), Jodrell Professor of Physiology in University College, London. 9th ed. Pp. 1155; 668 illus. Philadelphia: Lea & Febiger, 1945. Price, \$10.00.

Essentials of General Anæsthesia. By R. R. MACINTOSH, M.A., M.D., F.R.C.S., D.A., Nuffield Professor of Anæsthetics, Univ. of Oxford; Consult. Anæsthetist to the Royal Air Force; Anæsthetist to the Radcliffe Infirmary, Oxford; late Anæsthetist and Lecturer in Anæsthetics, University Coll. Hosp. Dental School; Anæsthetist, Golden Square Ear, Nose and Throat Hosp.; Assist. Anæsthetist, Guy's Hosp. Dental School; and FRED A. BANNISTER, M.A., M.D., D.A., First Assistant, Nuffield Dept. of Anæsthetics, Univ. of Oxford; Anæsthetist to the Oxford Eye Hosp.; late Clin. Assistant in Anæsthetics, University Coll. Hosp. Dent. School. 3rd ed., 2nd reprint. Pp. 341; 239 illus. Springfield, Ill.: Thomas, 1945. Price, \$5.50.

CORRECTION

On page 480 (April number) in the heading of the Progress Department of Dermatology and Syphilology, the name of JOHN STOKES, M.D., was unfortunately omitted. The lines should read: "Under the charge of John Stokes, M.D., Herman Beerman, M.D., and Norman R. Ingraham, Jr., M.D., Emeritus Professor and Assistant Professors, respectively, . . ." On page 490, 18 lines from the bottom of the first column, "of the skin" should be followed by "is the epidermal."

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